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ARCHIVES OF SURGERY

VOLUME 29 NOVEMBER 1934 NUMBER 5

PASSIVE VASCULAR EXERCISES

TREATMENT OF PERIPHERAL OBLITERATIVE ARTERIAL DISEASES BY RHYTHMIC ALTERNATION OF ENVIRONMENTAL PRESSURE

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AND
MONT R. REID, M.D.
CINCINNATI

The principal objectives in the treatment of obliterative arterial diseases are the relief of pain and the reestablishment of an adequate collateral circulation in the extremity. The active vascular exercises advocated by Buerger,[1] later modified by Allen,[2] as well as all forms of chemotherapy, physical therapy and surgery, contribute greatly to the patient's comfort. These measures, however, fail to bring about a complete or even an adequate restoration of the circulation in the majority of patients, especially in those suffering from extensive organic disease of the peripheral arteries.

It has long been known that the circulation of a part could be enhanced greatly by decreasing the environmental pressure, thereby decreasing the peripheral resistance to the flow of blood through the part. This principle was first utilized clinically by James Murray,[3] in 1812. Many reports concerning this method of treating acute and chronic inflammatory processes appeared during the past one hundred years. In 1905, Klapp[4] built an apparatus into which an entire extremity could be placed and treated by decreased environmental pressure. He reported excellent results in mobilizing stiffened joints after increasing the vascularization by means of the suction apparatus. In 1908, Willy Meyer and Schmieden[5] published a book entitled "Bier's Hyperemic

From the Department of Surgery, the University of Cincinnati College of Medicine, and the Vascular Disease Clinic of the Cincinnati General Hospital.

1. Buerger, L.: Circulatory Disturbances of the Extremities, Philadelphia, W. B. Saunders Company, 1924.

2. Allen, Arthur W.: Recent Advances in the Treatment of Circulatory Disturbances of the Extremities, Ann. Surg. **92**:931, 1930.

3. Murray, James: Nature and Treatment of Cholera: New Method Proposed, London M. & S. J. **1**:749, 1832; **2**:185, 1832; On the Local and General Influence on the Body of Increased and Diminished Atmospheric Pressure, Lancet **1**:909, 1835.

4. Klapp, R.: Mobilisierung versteifter und Streckung kontrakturierter Gelenke durch Saugapparate, München. med. Wchnschr. **52**:796, 1905.

5. Meyer, W., and Schmieden, V.: Bier's Hyperemia Treatment, Philadelphia, W. B. Saunders Company, 1908.

Treatment," in which they described and illustrated Bier's apparatus for bringing about an increase in the circulation in the extremities by means of suction. In 1917, Sinkowitz and Gottlieb[5a] reported excellent results in thrombo-angiitis obliterans with Bier's suction hyperemia treatment. In 1928, Dennis Jackson [6] of the department of pharmacology of the University of Cincinnati designed and built a special metal boot, with small windows in it, for the application of suction to the lower extremities, but as far as can be determined the boot was never used for clinical purposes. Braeucker [7] published an interesting article on the treatment of Raynaud's disease by creating a partial vacuum about the affected extremity. He illustrated and described his apparatus in detail, and reported excellent results from this form of treatment in nineteen patients with Raynaud's disease. He stated that the patients remained free from symptoms after from four to eight weeks of intensive treatment.

In August 1932, we [8] completed an apparatus with which we were able to create an environment of intermittent negative pressure about an extremity. That apparatus was constantly modified and improved until, in February 1933, we constructed the original Pavaex research unit. The apparatus is entirely automatic, and will rhythmically change the pressure within the treatment chamber to any selected degree and at any selected rate of alternation. It was through the use of the automatic apparatus [9] for over a thousand treatments that we were able to collect sufficient clinical and experimental data to prove beyond doubt that the rhythmic exchange of pressure from about 80 mm. of mercury negative pressure to about 20 mm. of mercury positive pressure is responsible for the development of an adequate collateral arterial circulation. In the last analysis the treatment consists of passive vascular exercises, which, when carried out frequently enough, cause the smaller arterioles to dilate and become sufficiently large to carry on the collateral circulation about the obliterated or badly diseased arteries.

5a. Sinkowitz, S. J., and Gottlieb, I.: Thrombo-Angiitis Obliterans: The Conservative Treatment by Bier's Hyperemia Suction Apparatus, J. A. M. A. **68**: 961 (March 31) 1917.

6. Jackson, Dennis E.: Personal communication to the authors, July 7, 1932.

7. Braeucker, W.: Die Behandlung der Raynaudschen Krankheit, Chirurg. **3**:756 (Sept. 1) 1931.

8. (*a*) Reid, Mont R., and Herrmann, Louis, G.: Treatment of Obliterative Vascular Diseases by Means of an Intermittent Negative Pressure Environment, J. Med. **14**:200 (June) 1933. (*b*) Herrmann, Louis G., and Reid, Mont R.: The Pavaex (Passive Vascular Exercises) Treatment of Obliterative Arterial Diseases of the Extremities, J. Med. **14**:524 (Dec.) 1933.

9. Prior to the use of this automatic apparatus the manually controlled unit, as described and illustrated in previous publications, was used for over two thousand and six hundred treatments. The basic principle is the same in both types of apparatus.

In February 1933, Landis and Gibbon [10] published a preliminary note on the effects of alternate suction and pressure on the circulation in the lower extremities of a normal subject. They employed from 100 to 120 mm. of mercury negative pressure for twenty-five seconds, followed by from 80 to 120 mm. of mercury positive pressure for five seconds. The skin temperature was measured to detect changes in the blood flow. Landis [11] later stated that they were gathering some interesting and important data concerning the actual increase in the blood flow as brought about by the method of alternate suction and pressure. Until that time, however, they had confined themselves to the problem of discovering the most efficient method of applying negative and positive pressure, with the plan to use that information later in the treatment of patients. Such fundamental physiologic studies will undoubtedly place this form of treatment on a sound scientific basis.[11a]

THE PAVAEX (PASSIVE VASCULAR EXERCISE) APPARATUS

For the purpose of studying the effect of various amounts of negative and positive pressure and various rates of alternation on all forms of obliterative arterial diseases we designed and built an apparatus which we called the Pavaex research unit. The apparatus (fig. 1) consists of a control box and a chamber into which the extremity is placed. A specially constructed door on one side of the treatment chamber is designed to permit calorimetric and oscillometric studies to be made while the extremity is subjected to various amounts of negative or positive pressure. The construction of this chamber has been described in detail in previous publications.[12] The control box (fig. 2) of the unit houses all the mechanical and electric equipment necessary for the automaticity of the alternation of pressures. The unit was designed for the treatment of several patients at one time (capacity for six patients); consequently, separate sources of suction and pressure have been provided. In the Vascular Disease Clinic of the Cincinnati General Hospital the source of suction is a Worthington vacuum pump, with a capacity of 10 cubic feet (0.28 cubic meter) of air per minute at 26 inches (66.04 cm.) of mercury negative pressure. The pressure is supplied from the compressed air line of the hospital. The pressure and suction lines are connected to the control box by flexible heavy rubber tubes. The flexible tube to the treatment chamber passes out the opposite side of the control box.

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10. Landis, E. M., and Gibbon, J. H.: Effects of Alternate Suction and Pressure on Circulation in the Lower Extremities, Proc. Soc. Exper. Biol. & Med. **30**:593 (Feb.) 1933.

11. Landis, E. M.: Personal communication to the authors, May 16, 1933.

11a. Since this article was written a report of the important work of Landis and Gibbon has appeared in the Journal of Clinical Investigation. Reference will be made to that work in a subsequent publication.

12. Herrmann, Louis G.: Syphilitic Peripheral Vascular Diseases: Treatment by Means of an Intermittent Negative Pressure Environment, Am. J. Syph. **17**: 305 (July) 1933. (*b*) Reid and Herrmann.[8a] (*c*) Herrmann and Reid.[8b]

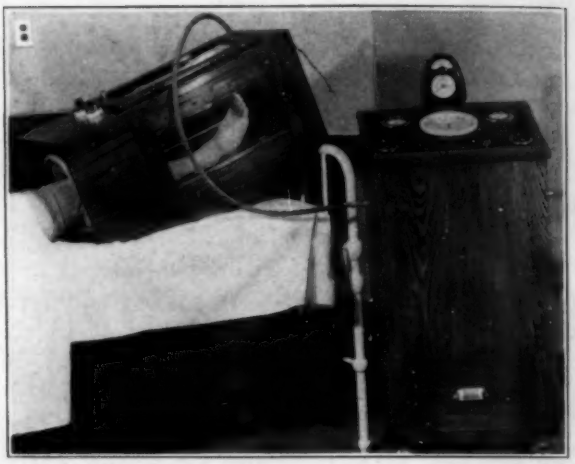

Fig. 1.—The original Pavaex Research Unit connected with the treatment chamber. Note that the extremity is elevated several inches above the level of the patient's heart.

Fig. 2.—The control box of the original Pavaex apparatus, showing the connections with the main supply of negative and positive pressure.

The control panel (fig. 3) carries the following objects: the dial in the upper left-hand corner which shows the amount of suction present in the main system at all times; the corresponding dial on the opposite side showing the amount of pressure present in the main system at all times; the knob below the suction dial which controls the rate at which air is withdrawn from the treatment chamber; the corresponding knob on the other side which controls the rate at which air is permitted to enter the treatment chamber; the large dial in the center which shows exactly the amount of positive or negative pressure existing within the treatment chamber at all times; the main switch on the left which controls the supply of current to the control box, and the corresponding switch on the other side which controls the current to the electric motor which drives the vacuum-pump.

Fig. 3.—The control panel of the original Pavaex apparatus. The large dial in the center shows the actual amount of negative or positive pressure which is present in the treatment chamber at all times during the treatment.

An amber light is connected in each of the circuits in order that one can be certain at a glance that the current has been turned on and the apparatus is ready to function. The two sets of contact-points are the selectors for negative and positive pressure, respectively. With them it is possible to produce any amount of positive or negative pressure within the treatment chamber from 5 to 120 mm. of mercury at steps of 5 mm. of mercury. When there is negative pressure in the treatment chamber a green light is energized, while a red light is energized when the pressure changes to the positive side. An electric interval clock is mounted on the control box in order that the rate of alternation and the duration of the treatment can be determined accurately. The apparatus is efficient and accurate and can be operated by a trained assistant. The patients who have been treated

exclusively by this apparatus have shown a rapid improvement in both subjective and objective findings. A simpler form of the apparatus is being manufactured commercially,[13] so that adequate treatment can be given in the home, office or small hospital.

METHOD OF TREATMENT

The patient is placed on a bed or cot, and the extremity to be treated is inserted through a soft rubber cuff into the treatment chamber (fig. 1). Large windows are so arranged that the color of the foot and leg can be observed at all times. A small amount of soap is rubbed on the inside of the glass windows, and the glass polished with a soft, dry cloth, so that moisture will not collect on the glass during the treatment. The foot and leg are then elevated several inches above the level of the heart. The treatment chamber is connected to the control box by means of a thick-walled rubber tube. The two main switches on the control panel are turned on, and the selector switches set for 80 mm. of mercury negative pressure and 20 mm. of mercury positive pressure. The rate of alternation is controlled by the knobs just below the main suction dial and main pressure dial on the control panel (fig. 3).

The apparatus automatically changes the pressure within the treatment chamber from the selected amount of negative pressure to the selected amount of positive pressure and at the rate of alternation desired. The average rate of one such cycle is about fifteen seconds. It has been our experience that in patients with high degrees of obliteration the first few treatments should be given with the alternation requiring about one half minute for completion of the cycle. As the circulation improves the rate of alternation is slowly increased until the entire cycle takes place within about fifteen seconds. For patients with extensive obliterative vascular disease with impending gangrene of the distal portions of the extremity we believe that it is necessary to hospitalize the patient and give four or five treatments (lasting for twenty minutes each) every day until the circulation of the foot shows definite signs of improvement. In our experience, striking changes in the circulation become established after two weeks of such intensive treatment. For the patient with intermittent claudication as the major complaint two treatments each day (for twenty minutes each) give satisfactory results in relieving them of pain and in restoring the circulation to an adequate level.

REPORT OF CASES

Fifty-one patients with organic obliterative arterial disease of one or more extremities have received regular and intensive treatment by this method. Thirty-two of these patients had a high degree of peripheral (senile) arteriosclerosis without evidence of gangrene; five had trophic lesions of one or more toes together with moderately severe diabetes mellitus; six had extensive organic arterial disease of the thrombo-angiitis obliterans type, and all six had one or more gangrenous digits of the hands or feet; four had syphilitic obliterative arteritis of the endarteritic or of the thrombo-arteritic type,[12a] and four had atypical arterial disease of the obliterative type. The clinical diagnosis in all

13. This apparatus is being manufactured by the Cincinnati Scientific Company, 224 Main Street, Cincinnati.

cases was confirmed by complete vascular studies before and after vasomotor relaxation under controlled conditions of temperature and humidity. Cases of pure vasomotor disturbances have not been included in this series.

Since August 1932, we have given three thousand, seven hundred and sixty-nine treatments by the Pavaex apparatus. Over three thousand of the treatments have been given to the fifty-one patients with organic obliterative arterial disease. Forty-six of the patients required treatment for both lower extremities.

One patient in the group with extensive (senile) arteriosclerosis was seen in consultation with Dr. J. L. Tuechter because of acute arterial thrombosis accompanied by excruciating pain and physical signs of marked ischemia of the right foot and leg. Complete vascular studies showed that the occlusion was organic and not the result of vasospasm. The patient was treated vigorously for periods of twenty minutes five times each day for two weeks, in the meantime being kept at complete rest in the hospital. The circulation improved rapidly, and the pain disappeared after three days of treatment. After about five days the toes retained the normal pink color between treatments. The patient was able to lie flat in bed with his lower extremities on the level with his heart after seven days of treatment. After leaving the hospital the patient continued to receive treatments at irregular intervals, but never more than one week apart, for three months. Recently he went hunting, walking for several hours without experiencing real discomfort. The severe intermittent claudication which was always present after slight exertion before the treatments were given has been completely relieved.

It is difficult, at present, to express in mathematical terms the benefits which have been derived from this form of therapy. The multiplicity of signs and symptoms (discoloration of the toes, subjective and objective sensation of cold extremities, aching or burning pains in the feet, easy fatigue of the muscles of the extremities, pain in the feet while at rest or intermittent claudication) which are directly or indirectly the result of organic disease of the peripheral arteries accounts in part for this difficulty. A careful analysis of the results obtained in the fifty-one patients reported in this work gave us the following data: In all the patients who received intensive treatment for two weeks or longer there was a definite increase in the surface temperature of the extremity when observed under controlled conditions of temperature (20 C. [68 F.]) and humidity (50 per cent). Forty-four of the patients (86.27 per cent) stated that most of the pain disappeared after about twenty-five treatments of twenty minutes each extended over a period of about two weeks. Six patients (11.76 per cent) showed only slight symptomatic relief after more than two months of treatment. One patient (1.97 per cent) stated that the pain was not influenced by three months of treatment, and no other cause for the patient's pain could be found. Four patients with moderately severe peripheral arteriosclerosis who were treated three times a week for

eleven weeks stated repeatedly that definite subjective and objective evidence of an increase in the circulation in the extremities remains for about forty-eight hours after each treatment. We are not prepared to give any information concerning the permanency of this increase in the circulation. We are, however, of the opinion that this form of treatment should be carried out over a period of many months if a permanent increase in the circulation is to be established.

It is highly important that patients with organic disease of the peripheral arteries continue to practice those measures for the general care of the feet which have been repeatedly emphasized by Allen [2] and by Reid.[14] Treatment with the Pavaex unit should supplement the methods which experience has shown to be of utmost importance in preventing infection from entering into the poorly nourished tissues of patients with peripheral vascular diseases. Forthcoming publications will give detailed reports concerning the results of treatments with the Pavaex unit in other types of obliterative arterial diseases.

SUMMARY

All therapy for obliterative vascular diseases should be directed primarily toward the establishment of a collateral circulation of sufficient magnitude to furnish proper nourishment to the distal portions of the extremity.

Rhythmic alternation of the environmental pressure about an extremity can be brought about automatically by the Pavaex apparatus.

The Pavaex treatment is essentially a mechanical means of performing passive exercises of the vascular system, i. e., passive vascular exercises.

A total of three thousand, seven hundred and sixty-nine treatments with the Pavaex unit have been given up to July 1933. Over three thousand of the treatments have been given to the fifty-one patients reported in this article.

Calorimetric evidence of an increase in the circulation in the distal parts of the extremities occurred in all fifty-one patients of the series, yet 13.73 per cent received little or no relief from their symptoms.

Forty-four patients (86.27 per cent) were greatly benefited by this form of therapy.

We believe that treatment with the Pavaex unit (passive vascular exercises) is the most effective means of bringing about the development of an adequate collateral circulation in the extremities of patients with extensive organic obliterative arterial disease.

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14. Reid, Mont R.: The General Care of Peripheral Vascular Diseases, Ann. Surg. **96**:733, 1932.

THROMBOSIS OF THE SIGMOID OR LATERAL SINUS

REPORT OF THIRTY CASES

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DETROIT
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There is a difference of opinion in this country and in Europe regarding treatment of otitic sinus thrombosis. Dandy [1] questioned the necessity for ligation of the jugular vein or an attempt to remove an infected clot. Mygind [2] reported his results in two groups of patients with otitic sinus thrombosis who were treated by different methods. The first group included 98 patients observed during the period from 1915 to 1922, with recovery in 55 per cent. The treatment of these patients was: (1) diagnostic puncture of the infected sinus, (2) removal of the thrombus and (3) ligation of the jugular vein. Mygind's second group of 101 patients observed during the years from 1923 to 1930 were treated more conservatively, and 71 per cent recovered. In 93 of the 101 patients the infected mastoid cells were thoroughly opened, but nothing was done to the sinus or vein: 70 of these 93 patients recovered without further surgical measures. On the other hand, Portmann [3] reported from Bordeaux that cases observed in a five year period showed 100 per cent of recoveries. When the clinical symptoms suggest a sinus thrombosis, Portmann (1) cleans out the mastoid, (2) ligates the jugular vein, (3) removes the clot and (4) obliterates the lumen of the sinus, even when the part of the sinus wall exposed at operation looks normal. During the past twenty years only 30 patients with otitic sinus thrombosis have been treated at the Johns Hopkins Hospital, and an analysis of the symptomatology and end-results in this group clearly shows that each patient must be studied as an individual, and that no dogmatic set of rules for either diagnosis or treatment is justifiable. The small number of cases in our series also illustrates the infrequency of this complication in Baltimore, since an average of 15,000 patients with diseases of the

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From the otolaryngologic service of the Johns Hopkins Hospital.

1. Dandy, W. E., in Lewis, D.: Practice of Surgery, Hagerstown, Md., W. F. Prior Company, Inc., 1932, vol. 12, chap. 1, p. 441.

2. Mygind, S. H.: Treatment of Otogenic Sepsis and Sinus Thrombosis, Acta otolaryng. **16**:474, 1931.

3. Portmann, G.: Considérations sur le traitement de phlébites et thrombophlébites sinuso-jugulaires, Rev. de laryng. **52**:523 (Oct. 15) 1931.

nose, throat and ear are seen in a year in the outpatient department of this hospital.

In our series of 30 patients with proved thrombosis of the lateral or sigmoid sinus, 66 per cent recovered. More than half of the group (16) were children under 14 years of age. The youngest patient was an infant, aged 1 year, and the oldest was 64. There was a history of acute otitis media in every patient. In the majority the onset of symptoms began with an earache two or three weeks before admission to the hospital. In 9 patients, however, a chronic suppurating otitis media had been present for several years, and a cholesteatomatous formation was probably responsible for the complications. A simple mastoid operation on 3 of the patients had failed to stop the purulent discharge from the ear, and it is possible that a more radical operation when the cholesteatoma first appeared would have prevented the infection of the sigmoid sinus. We feel that as a general rule a cholesteatoma should be treated radically, but the destruction of useful hearing in an attempt to cure a chronic discharging ear and thus prevent possible complications is not justifiable. In the great majority of our patients the sinus thrombosis was a complication of acute otitis media and mastoiditis. In 4 cases there is a note in the history stating that a definite cholesteatoma was present in the mastoid; 3 of the patients were adults over 33 years of age, and one was a child, aged 3 years.

For diagnostic purposes the following points should be noted:

1. A septic temperature was present in only 20 of our 30 cases. In a patient who recovered the temperature varied from 97 to 107.2 F. before operation. In several patients who recovered with no complications the temperature remained septic for as long as a week, and chills continued from two to five days after the operation on the mastoid, the excision of a portion of the sinus wall overlying the thrombus to provide drainage, partial removal of the thrombus and ligation of the jugular vein.

2. Shaking chills or chilly sensations were observed in 15, or 50 per cent, of our 30 patients. It is worthy of note: (1) that 7 (44 per cent) of the 16 children under 14 years of age had chills and (2) that 13 (87 per cent) of the 15 patients who had chills completely recovered, while only 7 (47 per cent) of the 15 patients who did not have chills recovered. This indicates that chills in a general septicemia may be a favorable prognostic symptom.

3. A positive blood culture is of decisive diagnostic value, but a negative culture does not rule out a sinus thrombosis. In our series blood was taken on admission from an arm vein in 21 patients. A culture gave no growth in 12 cases and positive results in 9. Postoperative blood cultures were made in 23 cases and were positive in 12. The hemolytic

streptococcus was the organism most frequently found (15 cases); a nonhemolytic streptococcus was found in 2 cases; the pneumococcus type III was found in 1 case, and the proteus bacillus in 1 case in which the blood was aspirated directly from the infected sinus. These results suggest that the constitutional symptoms (chills and septic temperature) may in some instances be due to absorption of toxins, and that the operative manipulations may disseminate organisms from the original focus.

4. The eyegrounds were examined in 26 patients. No change was noted in 9 patients, and a fulness of the veins in 5, but definite changes, varying from a haziness of the outlines of the nasal margin of the disk with distended veins to a swelling of 4 diopters, were found in 12 patients. The choked disk was limited to the side with the infected ear in 2 patients and was bilateral in 10. The changes in the fundus when bilateral are probably due to increased intracranial pressure and when unilateral to an extension of the infection through one or both of the petrosal sinuses to the cavernous sinus. The presence of either a bilateral or a unilateral choked disk is not necessarily a serious sign, since 4 of our patients with bilateral choking and 1 with unilateral choking recovered after the infection in the mastoid and in the sinus was drained.

5. A lumbar puncture for diagnostic purposes was limited as far as possible to patients with clinical signs of meningitis. The use of lumbar puncture and pressure on the jugular veins to locate the site of the thrombosis is associated with a certain amount of risk of a meningeal infection in patients with general septicemia. In our series of 30 patients only 12 had a lumbar puncture. In 5 the spinal fluid was normal; in 1 there was an increased cellular content with no increase of pressure, and 3 patients had purulent meningitis when admitted to the hospital.

REPORT OF CASES

A short résumé of the history and examination of each patient follows, and for convenience the cases are divided into three groups.

Group I comprises 2 patients with chronic suppurative otitis media who had undergone an operation on the mastoid several years prior to the present illness (cases 1 and 2).

Case 1.—In 1926, L. D., aged 46, had a radical mastoidectomy because of a chronic discharge in the right ear and the formation of a cholesteatoma. The discharge continued without general symptoms until Feb. 2, 1930, when the patient suddenly felt a severe pain in the right ear and the right side of the face; ethmoidal infection was present and was treated locally, but the pain became worse, and on February 8 she had a severe chill with delirium which lasted one-half hour. On the following day she had another chill and was admitted to the hospital; the temperature was 105.2 F. (rectal). Physical examination gave negative results except for a bilateral ethmoid infection and a purulent discharge in the right

auditory canal. The white blood cells numbered 9,800; hemoglobin was 84 per cent. Blood culture on February 11 showed 8 colonies of hemolytic streptococci per cubic centimeter, and three days later 26 colonies per cubic centimeter. The mastoid was opened on February 15, and the lateral sinus was exposed. The sinus was thickened and grayish white. The sinus was opened, and a suppurating thrombus was removed. The internal jugular and anterior facial veins were ligated. Transfusions were given; an infected thrombus of the internal saphenous vein, which suppurated, developed; later pneumonia developed. Convalescence was prolonged, but eventually the patient completely recovered.

Case 2.—M. B., aged 17, was treated nine years previously for chronic tuberculous infiltration of the lungs, and eight years previously had a simple right mastoidectomy. The patient continued to have intermittent attacks of right otalgia and otorrhea. The illness in question began two days before admission, with pain in the right ear and chills. The severe pain continued, but the discharge from the ear became less. The patient was admitted to the hospital on Oct. 3, 1927. Physical examination gave negative results except for a subperiosteal abscess of the right mastoid. The eyegrounds were normal except for fulness of the veins. The temperature rose to 107.4 F. The white blood cells numbered 16,400, and blood cultures taken on October 3 and 5 were sterile. The abscess was drained on October 3, but the septic temperature continued, and two days later the lateral sinus was exposed. A perisinuous abscess was found, and the lateral sinus was thrombosed. The sinus was opened, and the thrombus removed, but the jugular vein was not ligated. The patient made an uneventful recovery.

Group II comprises 6 patients referred to this hospital with evidence of septicemia following a simple mastoid operation (case 3 to 8).

Case 3.—In D. M., aged 10 years, following acute tonsillitis acute right otitis media and mastoiditis developed; simple mastoidectomy was done at his home in North Carolina on May 5, 1928, and he was kept under observation in the hospital until the ninth day. Six days later he became drowsy. The temperature was 104 F. The white blood cells numbered 6,000, and malarial parasites were found in the blood, but there was no improvement with quinine therapy. On May 22, a blood culture showed hemolytic streptococci, and on the following day the patient was given a transfusion of 500 cc. of blood. The child was admitted to the Johns Hopkins Hospital on May 28. Physical examination gave negative results. The white blood cells numbered 13,900. The temperature was 104 F. The blood cultures which were taken on May 28 grew hemolytic streptococci. The right mastoid was reopened and the lateral sinus exposed. Pus was found around the jugular bulb; the sinus wall was incised, and the thrombus removed. The internal jugular vein was found collapsed and was ligated. The patient was given transfusions and made an uneventful recovery.

Case 4.—In D. C., aged 4 years, bilateral acute otitis media developed on April 1, 1928. The drums were incised, and the ears discharged profusely, but the patient did not improve. On April 28 at the local hospital a bilateral simple mastoidectomy was done, but the temperature continued to fluctuate between 99 and 106 F., and there were chilly sensations. On May 8 a blood culture was sterile, and the patient was given a transfusion of 500 cc. of blood. When admitted to this hospital, on May 11, he was irritable. The physical examination gave negative results. The temperature was 102.2 F. The white blood cells numbered 17,500. There were a purulent discharge in the auditory canals and a slight discharge in both mastoid wounds. A culture of the blood grew hemolytic streptococci. The patient

had a chill shortly after admission. The mastoids were reopened, and the lateral sinus was exposed. On the left side the sinus appeared normal, but on the right side a pocket of pus was found near the jugular bulb. The sinus was thrombosed, the wall incised, the thrombus removed and the internal jugular vein ligated. The patient was given transfusions, and on May 24 a culture of the blood showed 20 colonies of hemolytic streptococci per cubic centimeter. An abscess of the hip developed and was incised, which showed Staphylococcus aureus. The patient improved and was discharged well.

Case 5.—J. V., aged 3 years, on April 21, 1924, suddenly felt pain in the right ear. The drum was incised and the ear discharged, but fever continued, and pain developed behind the right ear. On May 18 a simple mastoidectomy on the right was done, and the child improved slightly for four days. The temperature gradually became elevated, and the patient became delirious. Mercurochrome was given intravenously. The temperature became intermittently high and three days before admission a swelling of the right groin developed. The patient was admitted to the hospital very ill and irritable, with poor color; the eyegrounds showed choked disks; the liver was enlarged, and there was an abscess of the left hip and the right ankle. The white blood cells numbered 13,300. The hemoglobin was 48 per cent. The temperature was 103.2 F. A blood culture was sterile. The mastoid was reopened on May 31, and the lateral sinus was exposed and incised, but no thrombus was demonstrable. The internal jugular vein was ligated, and the left drum was incised, with a liberation of pus. The left hip and right ankle were opened and drained. The child remained in a poor condition with a septic temperature. Transfusions were given. A culture of the blood on June 2 was sterile. The patient died on the fourth day. Autopsy revealed a thrombosis of the right lateral sinus.

Case 6.—V. G., aged 4 years, had a sore throat on May 5, 1928, and pain in the left ear one week later. The drum was not incised, and swelling and redness of the left mastoid region were noted on May 16. Pain and moderate fever continued, and simple mastoidectomy on the left was done on May 20, with some improvement for two days. On May 26 a septic temperature developed, and the child was admitted to this hospital, ill and weak, with bilateral choked disks, a positive Kernig sign and a mastoid wound filled with granulations. The temperature was 105.4 F. The white blood cells numbered 18,200. The blood culture taken on May 26 showed 30 colonies of hemolytic streptococci per cubic centimeter. The mastoid was reopened on the day of admission. The sinus was exposed, incised and found to be thrombosed from above the knee to beyond the subclavian. The thrombus was entirely removed at the upper end, but the lower limit could not be reached. The child grew progressively worse in spite of transfusions. On May 27 a blood culture grew 3,200 colonies of hemolytic streptococci; on May 28, 240 colonies; May 29, 6,000 colonies, and on May 30, 400 colonies; in the last instance the blood was taken immediately following a transfusion. The spinal fluid was clear, with no increase of cells or pressure. Pneumonia developed, and the patient died on June 1, 1925.

Case 7.—M. D., aged 2½ years, three weeks before admission had influenza and tonsillitis, followed by pain and discharge in the left ear. Two weeks after onset simple mastoidectomy was performed on the left, and after the operation the patient had a septic temperature. A red, swollen area developed on the calf of the left leg, and later the left hip became swollen and tender with fixation and internal rotation. The patient was admitted to this hospital on March 24, 1933, ill and restless. The general examination gave negative results except for the bulging of the left drum; the mastoid wound was open; the right drum was red and full,

and the left thigh was swollen with adduction and internal rotation of the left hip. The temperature was 102.2 F. The white blood cells numbered 25,000. The left hip was incised and drained the following day, and a culture yielded hemolytic streptococci. The mastoid was reopened on March 26, the lateral sinus was exposed and incised, and a partial thrombus was removed; the internal jugular vein was ligated and cut. The patient grew progressively worse. A blood culture on April 2 grew hemolytic streptococci; the spinal fluid showed evidence of meningitis and on culture grew hemolytic streptococci. The patient died on April 3.

Case 8.—E. E., aged 18, had a simple mastoid operation on the right in 1928, and since then had had an intermittent discharge from the ear. Four weeks before admission a cold in the head and sore throat with delirium and pain and discharge in the right ear developed. She had an oscillating temperature, and the mastoid was opened on March 19, 1933. Chills and a septic temperature developed, and the mastoid was reopened on March 25; the lateral sinus was reported to look normal. When admitted to the Johns Hopkins Hospital on April 1, the patient was sick, thin and undernourished; the skin was dry. Physical examination gave negative results. The temperature was 103 F. The white blood cell count was 5,800; the hemoglobin, 75 per cent. The right mastoid was reopened on April 4, and the lateral sinus was exposed, incised and found thrombosed. The thrombus was removed and the internal jugular vein ligated. This girl had a long convaleseence, and was given several transfusions. Repeated blood cultures were sterile.

Group III is composed of 22 patients who were admitted with acute mastoiditis. Subgroup 1 comprises 6 of these patients, whose treatment consisted of a simple mastoidectomy (cases 9 to 14).

Case 9.—In B. W., aged 7 years, a sore throat developed four weeks before admission, and three days later pain in the right ear. The right drum was incised. Earache developed on the left side three days later, and the left drum was incised. The pain in the left ear persisted, and the discharge was much thicker than that from the right ear. Ten days before admission the child had pain over the left eye and temple and below the left ear, and two days before admission swelling and tenderness of the left mastoid were evident. The child was admitted on Feb. 27, 1932, not acutely ill. Physical examination gave negative results. There was a purulent discharge in the left auditory canal with swelling and redness of the left mastoid. A slight mucopurulent discharge was seen in the right auditory canal. The temperature was 100 F. The white blood cells numbered 14,900. The hemoglobin was 83 per cent. A blood culture was sterile. The left mastoid was opened and found to be filled with pus and granulations, and a large perisinuous abscess was found walled off by granulations. The lateral sinus was thrombosed, but it was not incised. The child made an uneventful recovery.

Case 10.—M. H., aged 25, was admitted unconscious, with a fracture of the skull and bleeding from the nose and ear. A subtemporal decompression was done on January 26, and nine days later a bloody purulent discharge from the right ear developed, followed in two days by swelling and tenderness of the right mastoid. A simple mastoidectomy on the right was done on February 6, and the lateral sinus was accidentally opened; it bled profusely, and was packed. On February 10 and February 17, blood cultures grew hemolytic streptococci. Spinal puncture revealed a clear spinal fluid. The patient died on February 18, and autopsy showed an infected thrombus of the lateral sinus, septicemia and multiple pulmonary emboli and abscesses.

CASE 11.—W. G., aged 3 years, had acute pain in the right ear three days before admission. The drum was incised, and the ear discharged; two days later a swelling developed in front of and behind the right ear. The patient was admitted on Feb. 28, 1933. Physical examination gave negative results except for edema and swelling above and anterior and posterior to the right ear, with projection of the auricle; the right auditory canal was filled with pus, and there were a pulsating perforation of the drum, large glands at the angle of the jaw and subacute tonsillitis. The temperature was 101 F. The white blood cells numbered 17,300. The subperiosteal abscess was incised and drained on March 3, and the mastoid was opened on March 10. The mastoid was filled with pus, granulations and necrotic bone, and on culture pneumococcus type III was grown. A large perisinuous abscess under pressure was found, and the lateral sinus was thrombosed but not opened. The patient made an uneventful recovery.

CASE 12.—B. M., aged 54, was seen in the dispensary on June 23, 1915, with a complaint of pain in the right temporal, mastoid and occipital regions of five weeks' duration. The right drum was incised, and pus was obtained. The patient had a chronic infection of the right frontal sinus, ethmoids and antrum, perforation of the palate and loss of the greater part of the septum. The symptoms continued, and the patient was admitted on July 6. The ethmoid cells and the right antrum were opened on July 8, and the mastoid was opened on July 13. The mastoid was dense and hard and contained a few small infected cells; the mastoid antrum was filled with pus and granulations. On admission examination revealed nothing except the changes already noted. The white blood cells numbered 7,500. The Wassermann reaction was negative, and examination of the spinal fluid and of a blood culture gave negative results. Following operation the temperature remained elevated; the spinal fluid was normal, and the eyegrounds revealed a choked disk on the right. The patient became irrational and died on August 2. Autopsy revealed necrosis of the right temporal bone and thrombosis of the right sigmoid and lateral sinuses.

CASE 13.—B. W., aged 64, had acute left otitis media eighteen years previous to admission which cleared up with no further trouble. Headaches developed four months previous to admission, and one month later pain in the left side of the head, fever and delirium were manifest. The patient was unconscious for two days. He then had an irregular fever, and weakness of the left arm was evident. Five weeks later he had a second attack with weakness and unsteadiness of gait, which increased; the left ear began to discharge. Five weeks before admission he noticed dimness of vision; he became irritable and emotionally unstable and lost 45 pounds (20.4 Kg.). He was admitted to the hospital on Aug. 7, 1924. Physical examination revealed a slight serous discharge in the left ear, moderate choking of the disks, a small hemorrhage in the left fundus and loss of the right corneal reflex; station and gait were unsteady, and true ataxia and weakness of the left arm were present. The Romberg sign was positive. The white blood cells numbered 10,200. A cerebellar abscess was found and evacuated; on culture it grew Staphylococcus aureus. A radical operation was done on the left mastoid on October 1, and a large cholesteatoma which had eroded into the posterior fossa was found; the lateral sinus was thrombosed, but it was not opened. The patient improved for a time, but pneumonia developed, and he died.

CASE 14.—M. M., aged 6 years, acquired a cold in the head and pain in the left ear on Feb. 26, 1925. There was no discharge from the ear. The patient had a high fever at night and became delirious on March 9. The drums were punctured with a needle on March 9 and again on March 12, but the patient had a chill during the evening of March 12 and was admitted to the hospital on

March 13. Physical examination gave negative results, except for bulging drums with a serous discharge from the left canal, marked tenderness of the left mastoid, bilateral choked disks and full veins and dilatation of the cutaneous veins over the forehead. The white blood cells numbered 19,800. The hemoglobin was 60 per cent. A blood culture was sterile, and the spinal fluid was clear, with a slight increase of pressure. The left mastoid was opened on March 14. The cells around the antrum were filled with granulations; the lateral sinus was incised and drained. The patient improved slowly and was discharged on April 3.

Subgroup 2 is composed of 7 patients whose treatment consisted of a simple mastoidectomy and ligation of the jugular vein (cases 15 to 21).

Case 15.—L. P., aged 4 years, had measles two weeks before admission, and eight days later pain in the left ear, but no discharge. A swelling developed behind the left ear two days before admission to this hospital, April 8, 1931. Examination disclosed a sick girl with acute follicular tonsillitis, a serous discharge in the left ear, a bloody discharge in the right ear and bilateral postaural swelling; the eyegrounds were normal. The temperature was 104 F. The white blood cells numbered 31,200. On April 9, incision and drainage of the subperiosteal abscesses were done. A blood culture was sterile. On April 12, a bilateral mastoidectomy was done, and pus and granulations were found in the mastoids. On the left side a small perforation of the sinus plate and a large perisinuous abscess were found; the sinus wall was collapsed and filled with pus. The thrombus was removed superiorly from the sinus, and the internal jugular vein was ligated. The temperature fell gradually to normal. The patient was given transfusions and had an uneventful recovery.

Case 16.—R. B., aged 54, had influenza with nausea and vomiting three weeks before admission; these were followed by a severe jumping pain in the left ear and severe headache. The left drum was incised and discharged, and on April 10, 1917, edema of the wall of the canal was noted, and he was admitted to the hospital on April 12. Physical examination gave negative results; the eyegrounds were normal, and there were discharge in the left auditory canal and edema of the posterior wall of the canal. The temperature was 102 F. The white blood cells numbered 12,600. The spinal fluid was clear, and the pressure was increased. A blood culture grew nonhemolytic streptococci, 10 colonies per cubic centimeter. The patient had a chill on April 14, and the mastoid was opened and found to be filled with thin, sticky pus and necrotic bone. The sinus plate was necrotic, and a perisinuous abscess was found. The lateral sinus was incised and bled freely. A mural thrombus was present, and the left internal jugular vein was ligated. The patient made an uneventful recovery, but nonhemolytic streptococci were grown in a blood culture on April 13 (2 colonies) and again on April 24.

Case 17.—C. C., aged 40, had pain in the right ear four weeks before admission, and the ear discharged pus two days later. Two weeks before admission she had marked nausea, felt hot and chilly at times and complained of a dull, throbbing headache of the right temporal and occipital regions. Following this she began to have dimness of vision, and her friends noted a drooping of the right upper eyelid. She was admitted to the hospital on Jan. 8, 1932. Physical examination gave negative results except for a purulent discharge in the right ear, a full drum with a small posterior pulsating perforation, eyegrounds which showed marked bilateral papilledema, with a few punctate hemorrhages and an exudate about the disks, and drooping of the right upper eyelid. The temperature was 102 F. The white blood cells numbered 15,000. A blood culture grew 1 colony of hemolytic streptococci from 2 cc. of blood. The right mastoid, which was opened on Febru-

ary 12, showed evidence of slight infection; a persinuous abscess was found around the lateral sinus, which was covered with granulations. The sinus was incised, and the thrombus removed; the internal jugular vein was ligated. The patient convalesced slowly. A blood culture on January 16 grew hemolytic streptococci, less than 1 colony per cubic centimeter. The ptosis of the right eyelid cleared up, and the papilledema subsided.

CASE 18.—B. F., aged 7 years, had had occasional attacks of otorrhea after typhoid fever three years previously, and during the past winter had several attacks of earache with a foul discharge from the ear. On Jan. 6, 1918, pain and discharge developed in the left ear; the patient had chills and fever daily and at night became delirious. He had a chill on January 11 and was admitted to the hospital on January 12. The temperature was 100.2 F. The left auditory canal was filled with a foul, purulent discharge. There were swelling and marked tenderness of the left mastoid and fulness and tenderness along the left internal jugular vein. The head rotated to the right; the muscles of the neck were spastic and the Kernig sign was positive. The patient was drowsy. The white blood cells numbered 26,200. A blood culture was sterile. Spinal puncture revealed a clear fluid, with a normal pressure and 20 cells. The left mastoid was opened on January 12 and found extensively involved; all of the bone was necrotic. A perisinuous abscess was found, and the wall of the sinus was nowhere intact. The lumen was filled with pus. An extradural abscess was found posterior to the sinus, and 1 ounce (31.1 cc.) of pus was evacuated. The jugular vein was found thrombosed almost to the clavicle and was ligated as low as possible; the thrombus was removed from the vein and the sinus. The temperature gradually fell to normal, and the patient was discharged well.

CASE 19.—B. W., aged 19, who was eight months pregnant, had an acute tonsillitis six weeks before admission, with pain in the right ear one week later. The drum ruptured spontaneously several days later, but the pain persisted, and she had a chill three days before admission and another on the day before admission. She was admitted to the hospital on Oct. 22, 1913. The temperature was 98 F. A physical examination gave negative results. There was no discharge in the right auditory canal. There were a small perforation of the drum, tenderness of the right mastoid and slight injection of the tonsils and pharynx. A blood culture grew hemolytic streptococci. The mastoid, which was opened on Oct. 23, 1913, was found to be infected; a perisinuous abscess was located. The lateral sinus was incised, and the thrombus was removed. The internal jugular vein was ligated and divided. The patient had an uneventful recovery. The child was delivered on the third day after operation, but died within seven hours. It is interesting to note that hemolytic streptococci were isolated from the placental and fetal circulation.

CASE 20.—J. C., aged 15, had a cold in the head followed on Feb. 26, 1933, by pain in the right ear. The pain became more severe, and the drum was incised on March 2; there was a profuse pulsating discharge. Pain then developed in the region of the tip of the mastoid. The patient was admitted to the hospital on March 6. Physical examination gave negative results. There were a profuse pulsating discharge in the right auditory canal and tenderness of the right mastoid and sternocleidomastoid muscle. The white blood cells numbered 11,500. A blood culture grew 1 colony of the pneumococcus type III per cubic centimeter. The Wassermann reaction was 4+, and the patient was given antisyphilitic treatment. The mastoid was opened on March 11; the cells at the tip of the mastoid were infected, and an extensive perisinuous abscess was found. The wall of the sinus

was incised, the thrombus removed and the internal jugular vein ligated. The patient had an uneventful recovery.

CASE 21.—In N. C., aged 10 years, ten days before admission a sore throat and acute right otitis media developed with nausea, vomiting and prostration. The patient became much worse and two days before admission had chills, fever, delirium and a severe rigor. She was admitted to the hospital on May 28, 1925. The temperature was 104 F. The patient was extremely sick and had a discharge in the right ear. The white blood cells numbered 7,000. A blood culture showed hemolytic streptococci. The right mastoid was opened on June 1, but it was not infected. The lateral sinus was exposed and incised; an infected thrombus was removed and the jugular vein ligated. The patient had a succession of metastatic abscesses in spite of transfusions, and she became thin and emaciated. Blood cultures on July 20 grew hemolytic streptococci. The patient died.

Subgroup 3 is composed of 9 patients who had a simple mastoidectomy followed by jugular ligation a few days later (cases 22 to 30).

CASE 22.—L. D., aged 8 years, had pain and discharge from the left ear five days before admission and on the following day pain and discharge from the right ear. The pain was more severe and the discharge more profuse from the left ear. He was admitted to the hospital on June 10, 1931, quite sick, with discharging ears. The white blood cells numbered 19,400. A blood culture was sterile. Mastoidectomy on the left was performed on June 13; the mastoid was infected, and the sinus plate was necrotic. A perisinuous abscess was found; the wall of the sinus was thickened. The temperature fell to normal following the operation, but at midnight June 14 it rose to 105.4 F. The blood culture remained sterile, and on June 15 the left internal jugular vein was ligated. The temperature gradually became normal, and the patient made an uneventful recovery.

CASE 23.—J. L., aged 12 years, had a right earache on April 12, 1929, and the following day the temperature was 105 F.; the drum was incised, and a thin, watery discharge was obtained. On April 22 the temperature was 105 F.; the child became mildly delirious and had a chill, but on the next day the temperature was normal. The patient was admitted to the hospital on April 24. Examination gave negative results. The temperature was 102 F. The white blood cells numbered 18,000. The blood culture was sterile. A serous discharge was present in the right ear, but there was no definite evidence of mastoid involvement. On April 27, the child had a chill, and the next day the temperature suddenly rose to 104 F. and fell to normal. Mastoidectomy was done on April 29. The mastoid cells were extensively diseased, especially in the zygomatic region and in the sinodural angle, but the lateral sinus was not exposed. Following this operation, the temperature remained normal for two days, and the blood culture was sterile; then a septic temperature with chills developed. On May 5, a blood culture grew hemolytic streptococci. The right internal jugular vein was ligated, and the lateral sinus was exposed; a thrombus was found in the jugular bulb. Tenderness of the sternoclavicular joint developed, which subsided. Otherwise the convalescence was normal.

CASE 24.—R. T., aged 14 years, had measles three weeks before admission and two weeks later a pain in the right ear with rupture of the drum and a profuse discharge. The earache became worse, the discharge continued, and the day before admission he had pain in the left ear. He was admitted to the hospital on May 2, 1931. The temperature was 103.2 F. The right mastoid was acutely tender, and there was a profuse, pulsating, mucopurulent discharge in the right auditory canal. The left drum was red and bulged. The white blood cells numbered 16,600.

Mastoidectomy on the right was done on May 3, and all the cells were found to be infected. Pus welled up when the cortex was opened. The lateral sinus formed the floor of the mastoid and appeared to be normal. The temperature remained elevated. A blood culture on May 7 grew less than 1 colony of hemolytic streptococci per cubic centimeter. The mastoid was reopened, but the sinus was not thrombosed. On the following day, the patient had a chill, and the temperature was elevated. On May 9, the left mastoid was opened and found to be filled with pus and granulations; the left lateral sinus was normal. The right internal jugular vein was ligated. The temperature fell to normal but suddenly rose to 105.6 F. on May 12. The blood cultures on May 18 and 28 were sterile. Bronchopneumonia developed. Convalescence was long, but the patient finally recovered.

Case 25.—J. S., aged 38, had an intermittent discharge from the right ear from childhood, and three months before admission a cold in the head and a more profuse and constant discharge from the right ear developed. The hearing in the right ear became progressively worse, and three days before admission pain developed in the region of the right mastoid and over the right side of the head. The patient was admitted to the hospital on April 2, 1917. The temperature was 100 F. General examination gave negative results. There were a purulent discharge in the right auditory canal and tenderness of the right mastoid. The white blood cells numbered 10,400. The mastoid was opened on April 3. A small perforation of the cortex which led to the lateral sinus was found; the cells were filled with thin pus, and the lateral sinus looked normal. The temperature fell to normal following the operation, but suddenly rose on April 8 to 103.6 F., and the blood culture grew 15 colonies of hemolytic streptococci per cubic centimeter. On April 9 the right internal jugular vein was ligated, and the lateral sinus was incised and bled freely. The blood culture on April 16 was sterile. A gluteal abscess developed which was incised and which on culture grew Staphylococcus albus. On April 24, a blood culture grew 2 colonies of nonhemolytic streptococci per cubic centimeter. The temperature fluctuated daily for two weeks. The patient was discharged well

Case 26.—E. H., aged 33, had a discharge and severe pain in the left ear of three months' duration, but no tinnitus or vertigo. She was admitted on Oct. 5, 1921. The temperature was 98 F. Physical examination gave negative results. There was a purulent discharge in the left ear, and the left drum was destroyed, with granulations in the middle ear. The white blood cells numbered 8,200. On October 6, the left mastoid was opened; the bone was densely hard, with no cells, and the antrum was filled with a cholesteatoma. The dura and the lateral sinus appeared to be normal. Following the operation the temperature remained normal, but on October 15 and 16 the patient had chills, with marked elevations of temperature. The white blood cells numbered 8,700. A blood culture grew nonhemolytic streptococci. Spinal puncture showed a clear fluid under normal pressure. The left internal jugular vein was ligated, and a thrombus was removed from the lateral sinus. The temperature remained elevated, and the patient became delirious with projectile vomiting. A lumbar puncture on October 19 showed 16 cells and another on October 20, 25 cells, and nonhemolytic streptococci were isolated on culture. The patient died.

Case 27.—S. S., aged 14 years, had chronic otitis media on the right of one year's duration. Bilateral acute otitis media with a purulent discharge developed two weeks before admission. The child could not walk straight and was unable to see plainly on sitting up; the patient was forced to go to bed, and for two weeks

had constipation and vomiting. He was admitted on May 26, 1930, very sick, and with his face flushed. The temperature was 104.8 F. There was a thick, purulent discharge in the auditory canals, swelling and tenderness of the left mastoid and bilateral papilledema. The white cell count was 20,800. A blood culture was sterile. On May 28, he had a subtemporal decompression and received an injection of air. The fluid was found to be under pressure, but otherwise was normal. On May 30, mastoidectomy was done on the left side; all of the cells were filled with a thick mucoid discharge, and the sinus plate was necrotic, with a large exposure of the sinus and a perisinuous abscess. The temperature remained low, but suddenly rose to 105.4 F. on June 1; on the next day the left internal jugular vein was ligated; the lateral sinus was incised, and the thrombus was removed. The temperature fell to normal in a week; the blood culture was sterile, and the patient had an uneventful convalescence.

Case 28.—L. L., aged 9 years, felt pain in the left ear on Feb. 8, 1924. The pain became progressively worse and the drum ruptured. The following week she was ill; the temperature was elevated irregularly, and there were loss of appetite and occasional vomiting. She became definitely more drowsy four days before admission; the temperature rose steadily and she was delirious at times. She was admitted on February 29. The temperature was 104 F. She was very ill, drowsy and weak. The left drum was injected and bulging; the mastoid was tender. There were bilateral choked disks and ankle clonus. The Kernig sign was positive on the right. A blood culture grew hemolytic streptococci, 70 colonies per cubic centimeter. A spinal puncture yielded a slightly turbid fluid under increased pressure and containing 750 cells. The white cells numbered 11,000. The left mastoid was opened on March 1, and a large area of the dura, which was more tense than normal, was exposed. The lateral sinus appeared to be normal. Lumbar puncture gave a cloudy fluid which contained 300 cells. The patient's condition remained unchanged. A blood culture on March 4 grew hemolytic streptococci, 15 colonies per cubic centimeter. The left internal jugular vein was ligated; the sinus, which was incised, bled freely. The temperature continued to fluctuate daily, and a blood culture on March 8 grew 60 colonies of hemolytic streptococci. The patient's condition grew progressively worse, and she died.

Case 29.—O. E., aged 1 year, was seen in the dispensary on April 19, 1915, with bilateral otitis media. The drums were incised. The condition in the right ear subsided, but the left ear continued to discharge. The child was admitted on May 14. The temperature was 103 F. There was a mucopurulent discharge in the left auditory canal, with a swelling above and behind the left ear. The white blood cells numbered 17,000. A blood culture was sterile. Mastoidectomy was performed on May 15, and free pus was found in all of the cells; the bone was necrotic, but the lateral sinus appeared to be normal. The child's condition improved; the temperature gradually fell to normal, but on May 21 it suddenly rose to 105 F. The white cells numbered 12,000. A blood culture was sterile. On May 22 the left mastoid was reopened; the sinus was incised and bled freely. The temperature gradually fell until May 27, when it began to rise daily, with fluctuation. On June 6, the blood culture grew numerous colonies of streptococci, and on the following day the lateral sinus and internal jugular vein were exposed and found to be thrombosed from the torcular herophili to beyond the clavicle; the thrombus was removed as far as possible, and the vein was ligated. The patient recovered.

Case 30.—D. T., aged 3 years, had chronic left otitis media, and was in a sanatorium for mediastinal tuberculosis. On Nov. 26, 1932, a pain in the left ear

with fever developed, and the paitent did not eat well. She was admitted on November 27. The temperature was 103.2 F. There was a foul, serous discharge in the left auditory canal; the drum had been destroyed, and débris and granulations were present in the middle ear. There was tenderness of the left mastoid. The white blood cells numbered 31,600. The eyegrounds were normal. On November 28 a subperiosteal abscess was incised, and a foul, serous discharge was obtained. The temperature fell to normal, but rose to 105.4 F. on December 1. A blood culture was sterile. The left mastoid, which was opened on December 1, was found to be filled with foul, pulsating, dirty pus. A perforation of the cortex and a cholesteatoma in the antrum were found. The lateral sinus was entirely an abscess cavity. Blood cultures taken on December 2 and 3 were sterile, but others made on December 5 grew hemolytic streptococci. The temperature became elevated on December 5. The internal jugular vein was ligated, and the lateral sinus was cleaned until bleeding ensued. In spite of transfusions, pneumonia developed, and the patient died. Autopsy revealed infected infarcts and abscesses of the upper and lower lobes of both lungs and empyema of the left lung.

TREATMENT

In the treatment of lateral sinus thrombosis no hard and fast rule can be established to govern every case. Each patient requires individual study, and the aim of the surgeon should be to make the diagnosis as accurately as possible and to institute such surgical therapy as is indicated.

In the Johns Hopkins Hospital the surgical treatment of sinus thrombosis varies with the severity of the clinical symptoms. A simple mastoidectomy is performed on all of the patients. A radical operation is performed on the mastoid only if hearing is markedly impaired owing to an extensive suppuration of the middle ear or to cholesteatoma. If there is clinical evidence of septicemia, a portion of the lateral and sigmoid sinus is exposed for direct inspection, and as a rule, the sinus is opened, the clot removed, and the jugular vein ligated. In the absence of clinical evidence of septicemia it is advisable to establish drainage and to wait rather than to make an exploratory incision or puncture of the sinus through an infected field. In the great majority of our patients, however, the clinical symptoms and the subsequent course seem to justify early ligation of the jugular vein.

In 21 patients with proved sinus thrombosis only a simple mastoidectomy was performed at the first operation:

1. In 9 of these patients the continued septic temperature and other clinical evidences of a spreading infection necessitated a second operation at which the sinus was opened, the clot removed and the jugular vein ligated; of these 9 patients 6 recovered; the fatalities in 2 cases were due to meningitis and in 1 case (case 30, table) to multiple pulmonary abscesses. It is doubtful that an earlier ligation of the jugular vein would have prevented the meningitis.

Summary of Thirty Cases of Sinus Thrombosis

Case	Age	Chills		Temperature Peak, F.	White Cell Count at Temperature Peak	Blood Culture	Colonies per Cc. of Blood	Eyegrounds	Spinal Puncture	Transfusions	Complications	Result
		Before	After									
1	46	Yes	Yes	105.2	9,800	Hem. str.*	26	Bilateral full veins*	Not done	Two, 500 cc. each	Bronchopneumonia; thrombosis of right internal saphenous vein	Recovered
2	17	Yes	No	107.4	16,400	Lateral sinus, Bacillus proteus	..	Bilateral full veins	Not done	None	None	Recovered
3	10	Yes	Yes	104.0	13,900	Hem. str.	..	Bilateral full veins	Not done	One, 250 cc.	None	Recovered
4	4	Yes	Yes	104.8	17,500	Hem. str.	20	Not examined	Not done	Four, 200 to 250 cc. each	Redness and swelling of right ankle; abscess of right hip	Recovered
5	3	No	No	105.0	13,300	No growth	..	Bilateral choked disks	Not done	Two, 175 cc. each	Abscess of right elbow and left hip	Died
6	4	No	No	105.6	18,200	Hem. str.	6,000	Bilateral choked disks	Normal	Two, 250 cc. each	Bronchopneumonia	Died
7	2½	No	No	105.0	21,000	Hem. str.	..	Bilateral full veins	Turbid fluid which grew streptococci	One, 160 cc.	Abscess of left hip; meningitis	Died
8	18	Yes	No	106.0	5,800	No growth	..	Normal	Not done	Six, 250 cc. each	None	Recovered
9	7	No	No	100.0	14,900	No growth	..	Normal	Not done	None	None	Recovered
10	25	No	No	105.0	.....	Hem. str.	25	Normal	Normal	None	Multiple pulmonary abscesses	Died
11	3	No	No	103.8	17,300	No growth	..	Not examined	Not done	None	None	Recovered
12	54	No	No	105.0	8,200	None	..	Right choked disk	Negative	None	Necrosis of right temporal bone	Died
13	64	No	No	99.0	10,200	None	..	Bilateral papilledema	Negative	None	Cerebellar abscess	Died
14	6	Yes	No	104.6	19,200	No growth	..	Bilateral choked disks	Pressure increased	None	None	Recovered
15	4	No	No	106.8	31,200	No growth	..	Normal	Not done	Two, 200 cc. each	None	Recovered
16	54	Yes	No	106.0	12,600	Nonhem. str.	10	Normal	Pressure increased	None	None	Recovered

17	40	Yes	No	103.0	15,000	Hem. str.	1	Bilateral papilledema	Normal	One, 450 cc.	Ptosis of right upper eyelid	Recovered
18	7	Yes	No	105.6	26,200	No growth	..	Not examined	20 cells	None	None	Recovered
19	19	Yes	No	104.0	11,200	Hem. str.	..	Veins full on right	Not done	None	None	Recovered
20	18	No	No	103.0	11,500	Pneumococcus type III	1	Right disk blurred on nasal side	Not done	None	None	Recovered
21	10	Rigor	No	106.0	7,000	Hem. str.	..	Both disks blurred on nasal side less on right	Not done	Four, 275 cc. each	Abscess of the left arm, left leg, parotids, hips and body	Died
22	8	Yes	No	105.6	19,400	No growth	..	Not examined	Not done	Two, 175 cc. each	Pain and redness of right knee	Recovered
23	12	Yes	Yes	104.0	18,000	Hem. str.	..	Normal	Not done	One, 200 cc.	Pain in right shoulder; redness and tenderness of sternoclavicular joint	Recovered
24	14	Yes	No	105.0	15,200	Hem. str.	..	Normal	Not done	Two, 250 cc. each	Bronchopneumonia; pain and redness of sternoclavicular joint	Recovered
25	38	No	No	103.8	12,600	Hem. str.	15	Normal	Not done	None	Gluteal abscess	Recovered
26	33	Yes	No	104.8	8,700	Nonhem. str.	..	Nasal margins of both disks blurred	25 cells; nonhemolytic streptococci	None	Meningitis	Died
27	14	No	No	105.2	15,000	No growth	..	Bilateral papilledema	Increased pressure	None	None	Recovered
28	9	No	No	106.5	11,000	Hem. str.	60	Bilateral papilledema	Increased pressure; turbid fluid, 750 cells	None	None	Died
29	1	No	No	106.0	16,000	Hem. str.	..	Normal	Not done	None	Abscess of leg	Recovered
30	3	No	No	105.4	25,000	Hem. str.	..	Bilateral hazy disks	Not done	Three, 125 cc. each	Multiple pulmonary abscess	Died

* Hemolytic streptococci.

2. In 6 of the patients the sinus was not opened, and the vein was not ligated; 3 patients recovered (50 per cent). The fatalities were due to multiple pulmonary abscesses (case 10), suppurative labyrinthitis (case 12) and a cerebellar abscess with terminal pneumonia (case 13).

3. Six patients had a simple operation on the mastoid before admission to this hospital. At a later date, varying from six to twenty-three days after the operation on the mastoid the sinus was opened, the thrombus removed and the jugular vein ligated; 3 patients (50 per cent) recovered. The fatalities were due to an overwhelming septicemia (6,000 colonies of hemolytic streptococci per cubic centimeter, case 6), pyemia with marked secondary anemia (case 5) and suppurative meningitis (case 7).

In 8 of the remaining 9 patients the mastoid was opened, the sinus incised, the clot removed and the internal jugular vein ligated at one operation. In 1 of these patients (case 2) the jugular vein was not ligated. The patient recovered. There was only 1 fatality in this group of 9 patients (case 21). Therefore 8 patients (89 per cent) in the group recovered.

PATHOLOGY AND ETIOLOGY

The hemolytic streptococcus is reported as the organism most commonly isolated in otitic sinus thrombosis. In our series this organism was grown from the blood in 15 patients, but from the mastoid wound in only 5; the nonhemolytic streptococcus was grown from both the blood and the mastoid in 2 patients; the pneumococcus type III was grown from the mastoid in 2 patients and from the blood in only 1. No patient in this series had staphylococcic septicemia.

A perisinous abscess was found in 14 of our 30 cases (47 per cent) in association with erosion of the bone overlying the sinus. In 3 patients thrombosis of the lateral sinus was found at autopsy, but its presence could not be demonstrated at operation. Acute otitis media was the first symptom in 21 patients, and in 9 patients there was an acute flare-up of chronic otitis media.

Sections made from a portion of the sinus wall excised at operation showed an acute inflammatory process and at times an infiltration with red blood cells. It is our impression that the progression of the thrombus is due primarily to the extension of the inflammatory process in the wall of the sinus or vein and not to an extension of the infection in the thrombus.

SUMMARY

1. Thirty patients with lateral sinus thrombosis are presented in this paper, 16 of whom were children under 14 years of age. Sinus thrombosis occurs in infancy (case 29) as well as in old age (case 13).

2. The syndrome of chills, a septic temperature and a positive blood culture are often absent. In this series 15 (50 per cent) of the patients had chills; 20 (66 per cent) of the patients had a septic temperature, and in only 9 (30 per cent) of the patients was a positive blood culture obtained before operation. Only 6 patients (20 per cent) had the combination of chills, a septic temperature and a positive blood culture before operation.

3. The white cell count, the temperature and the result of blood culture are shown in the table. A white cell count of 5,800 was associated with a temperature of 106 F. (case 8); a count of 8,700 with a temperature of 104.8 F., a positive blood culture and meningitis (case 26) and a count of 9,800 with a temperature of 105.2 and 26 colonies of hemolytic streptococci in the blood of a woman, aged 46 who recovered (case 1). As a rule, the blood count is higher in children than in adults.

4. The hemolytic streptococcus is the organism most commonly found in the blood in cases of otitic sinus thrombosis (50 per cent of our series). A culture from the mastoid or middle ear may give no indication of the organism in the blood stream, because the staphylococcus or other organisms frequently present in this location overgrow and prevent the recognition of the hemolytic streptococcus.

5. Following operation the temperature may remain elevated for as long as a week, but in uncomplicated cases the general direction of the curve is toward normal. A secondary abscess and pneumonia are the common causes of a continued septic temperature.

6. Chills were noted as a symptom in 15 patients. In 4 of these patients the chills continued for several days after the operation, which consisted of a simple mastoidectomy, incision of the sinus, removal of the thrombus and ligation of the jugular vein. In 3 of the 4 patients the continuation of the chills was probably due to a complication: pneumonia (case 1), abscess of the hip (case 4) and involvement of the sternoclavicular joint (case 23). In 1 patient, however, there were no complications to explain the continuation of the chills for four days (case 3).

7. Transfusions were used as a therapeutic measure in 14 patients. It is our impression that they are of decided value, provided the cross-matching is carefully done and the blood is given slowly enough to prevent severe systemic reactions. The number of patients who were given transfusions, the number of transfusions given and the more important clinical findings are shown in the table.

8. Ten patients in this series of 30 cases died, a mortality of 33 per cent; of the 20 patients (66 per cent) who recovered, 3 (15 per cent) had pain, redness and swelling around one or more of the joints, 2 (10 per cent) had isolated abscesses of the muscles of the leg, and 2 (10 per cent) had pneumonia. The complications are shown in the table.

VESICAL DISTENTION

II. EFFECTS ON THE MOTOR MECHANISM OF THE UPPER URINARY TRACT; AN EXPERIMENTAL STUDY

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The effects of distention of the urinary bladder on both the bladder itself and on the upper urinary tract have been studied and reported frequently in the past. Unfortunately, each investigator concerned himself with some isolated aspect of the problem, so that a coherent report of the process as a whole remains to be presented. For example, the changes which urethral ligature produces in the bladder, ureters and kidneys are well known. The mechanism by which these changes are produced has, however, remained relatively uncertain. Again, the question of the reflux of bladder urine into the ureters has been almost exhausted both experimentally and clinically; whether this phenomenon occurs in acute retention has been but little investigated. Also, research on the effects of rapid artificial filling of the bladder has led to results diametrically opposed, so far as the behavior of the kidneys and ureters is concerned.

It is the purpose of this article to present, in an orderly manner, the effects of urinary retention and of rapid artificial filling of the urinary bladder on the motor activity of the bladder and the ureters and to interpret their clinical significance. With this end in view, urinary retention was produced in the dog, and its effect on ureteral activity was studied. The function of the ureter during rapid artificial filling of the bladder was investigated, and a reflex, apparently not hitherto described, was discovered. This reflex evidently acts as an important mechanism, comparable to that which prevents urinary reflux, in protecting the upper urinary tract against sudden rises in intravesical tension.

REVIEW OF THE LITERATURE

The first phases of vesical distention to be well studied were the anatomic changes resulting from urethral ligature. Guyon and Albarran [1]

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1. Guyon, J. F., and Albarran, J.: Anatomie et physiologie de la rétention d'urine, Arch. de méd. expér. et d'anat. **2**:181, 1890.

obstructed the urethra of the dog and rabbit and observed the animals for periods up to seventy-two hours. They found that the chief anatomic changes consisted of hemorrhages, which appeared earliest in the vesical submucosa, spread later through the whole thickness of the wall of the bladder, and finally developed in the pelvis and parenchyma of the kidney. After from sixty to seventy-two hours the hemorrhages in the wall of the bladder led to necrosis, rupture and urinary peritonitis.

The occurrence of these changes was verified by the subsequent studies of Shigematsu [2] and of myself.

Guyon and Albarran stated that peristalsis disappeared from the ureter within twenty-four hours, while irritability to galvanism vanished within thirty-six hours. While Shigematsu's findings agreed with those of Guyon and Albarran, I have observed peristalsis even after seventy-two hours.

Guyon and Albarran observed progressive diminution in the urea content of the urine in each successive twenty-four hour period after obstruction had been established.

These are the only experimental studies which I have found which bear on the effects of urinary retention. For corroboration of these findings, one must review the literature of ureteral obstruction.

Cohnheim,[3] Lindemann,[4] Lucas,[5] Newman [6] and Winton [7] found that the flow of blood from the renal vein is diminished by distention of the renal pelvis. Fabian,[8] Corbett [9] and Helmholz and Field [10] ligated the ureters of the guinea-pig, dog and rabbit, respectively, and found that hemorrhages in the pelvic wall and renal parenchyma resulted. These observations may be combined to show that the retention of urine,

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2. Shigematsu, H.: Etude expérimentelle de la rétention d'urine, J. d'urol. **25**:16, 1928.

3. Cohnheim, J.: Vorlesungen über allgemeine Pathologie, Berlin, A. Hirschwald, 1880.

4. Lindemann, W.: Ueber die Wirkung der Gegendruckerhöhung auf die Harnsekretion, Beitr. z. path. Anat. u. z. allg. Path. **21**:500, 1897.

5. Lucas, D. R.: On the Intraureteral Pressure and Its Relation to the Peristaltic Movements of the Ureter, Proc. Soc. Exper. Biol. & Med. **2**:61, 1904; Studies of the Peristalsis of the Ureter in Dogs by the Graphic Method, Am. J. Physiol. **17**:392, 1906-1907.

6. Newman, D.: Residual Urine and the Senile Bladder, Glasgow M. J. **87**: 73, 1917.

7. Winton, F. R.: Influence of Increase of Ureter Pressure on the Isolated Mammalian Kidney, J. Physiol. **71**:381, 1931.

8. Fabian, E.: Die Niere des Kaninchens nach der Unterbindung ihres Harnleiters, Biblioth. med. Abt. Path. u. path. Anat. 1904, pt. 18, p. 1.

9. Corbett, J. F.: Changes in the Kidney Resulting from Tying the Ureter, Am. J. M. Sc. **141**:568, 1912.

10. Helmholz, H. F., and Field, R. S.: Acute Changes in the Rabbit's Kidney, Particularly the Pelvis, Produced by Ligating the Ureter, J. Urol. **15**:409, 1926.

whether in the bladder or in the pelvis of the kidney, interferes seriously with the blood supply of the urinary tract. That this is the case as concerns the kidney was demonstrated conclusively by Hinman and his co-workers.[11] They showed, chiefly by corrosion specimens, that a remarkable diminution in the size and number of the blood vessels of the kidney follows ureteral occlusion.

How are these changes produced? In order to answer this question it is desirable first to scrutinize the ability of the kidney and ureter, as well as of the bladder, to generate pressure.

It is difficult to establish the normal pressure relations in the urinary tract. Lucas,[6] from studies of the anesthetized dog (morphine), believed that the tension in the pelvis was usually negative, while that in the vesical end of the ureter might reach a few centimeters of water; he found that the excised ureter of a normal dog could exert a distending pressure of 92 cm. of water.

Beresnegowsky[12] observed individual peristaltic waves as high as 21 mm. of mercury in a woman with a ureterovaginal fistula. This cannot be regarded as normal, however, since such fistulas are usually associated with some fibrosis and hypertrophy of the ureter. Henderson[13] observed individual waves of 36 mm. in the dog.

Trattner[14] found that the pressure in the normal human ureter (ureteral catheter) ranged from 2 to 10 cm. of water.

The maximum pressure which may be generated by the normal kidney and ureter together has been thoroughly studied by allowing them to act against a rising vertical column of urine in a glass tube. The resultant tension has varied from a minimum of 40 or 50 mm. of mercury in the anesthetized dog (Heidenhain[15]) to a maximum of 76

11. Hinman, F., and Morrison, D. M.: Experimental Hydronephrosis, J. Urol. **11**:435, 1924. Hinman, F., and Hepler, A. B.: Experimental Hydronephrosis; Effect of Changes in Blood Pressure and in Blood Flow on Its Rate of Development; Partial Obstruction of Renal Artery; Diminished Blood Flow; Diminished Intrarenal Pressure and Oliguria, Arch. Surg. **11**:649 (Nov.) 1925; Experimental Hydronephrosis; Effect of Changes in Blood Pressure and in Blood Flow on Its Rate of Development, and Significance of Venous Collateral System; Partial Obstruction of Renal Vein Without and With Ligation of All Collateral Veins, ibid. **11**:917 (Dec.) 1925; Experimental Hydronephrosis; Effect of Ligature of One Branch of Renal Artery on Its Rate of Development; Simultaneous Ligation of Posterior Branch of Renal Artery and Ureter on Same Side, ibid. **12**:830 (April) 1926.

12. Beresnegowsky, N.: Zur Frage ueber die physiologische Tätigkeit der Ureteren, Zentralbl. f. Physiol. **22**:461, 1908.

13. Henderson, V. E.: The Factors of the Ureter Pressure, J. Physiol. **33**:175, 1905.

14. Trattner, H. R.: Ureteral Activity in Some Pathologic Conditions Studied by Graphic Manometric Method, Arch. Surg. **17**:968 (Dec.) 1928.

15. Heidenhain, R.: Die Harnabsonderung, in Hermann, L.: Handbuch der Physiologie, Leipzig, F. C. W. Vogel, 1881, vol. 5, pt. 1, p. 299.

mm. in the anesthetized rabbit during caffeine diureses (Gottlieb and Magnus [16]). Beresnegowsky [12] observed a tension of 70 mm. in an unanesthetized human female with a ureterovaginal fistula. Kreutzmann [17] found a maximum pressure of 66 mm. of mercury in the ureter during straining, making his measurements by means of a ureteral catheter passed through a cystoscope.

These studies refer only to pressures exerted by the normal pelvis and ureter. I have been unable to find data on those attainable with hypertrophied organs.

More information is available as to the potentialities of the bladder. Dubois [18] and Adler [19] found pressures of from 6 to 12 cm. of water (from 4.4 to 8.8 mm. of mercury) in the resting bladder. Estimates of the level which provokes the desire to void vary from 10 cm. of water (7.3 mm. of mercury)—Hirsch [20]—to 29.9 cm. of water (22 mm. of mercury)—Kreutzmann.[17] During micturition the tension averages 78 cm. of water (57.3 mm. of mercury), but may reach 86 cm. (63.2 mm.)—Schwarz and Brenner.[21]

Estimates of the maximum tension attainable by the normal bladder vary widely from 80 cm. of water (58.8 mm. of mercury)—Rose [22]—to 133 cm. of water (97.8 mm. of mercury)—Kreutzmann.[17]

One can gain from the literature only a vague idea as to the influence of obstruction of the vesical neck with its presumed hypertrophy of the wall of the bladder on the contractile power of the bladder. Many have recorded the intravesical tension during chronic and acute retention from this cause, but have neglected to make it plain whether, in a given case, the wall of the bladder was the seat of hypertrophy or atrophy. Many urologists claim to have seen the urine "shoot clear to the ceiling" when an obstructed bladder was opened or catheterized, but actual measurements in such circumstances have shown the pressure to range from 9 or 10 (Dubois [18]) to 50 cm. of water (Bumpus and

16. Gottlieb, R., and Magnus, R.: Ueber Diurese, Arch. f. exper. Path. u. Pharmakol. **45**:223, 1901.

17. Kreutzmann, H. A. R.: Studies in Normal Ureteral and Vesical Pressure, J. Urol. **19**:517, 1928.

18. Dubois, P.: Ueber den Druck in der Harnblase, Deutsches Arch. f. klin. Med. **17**::148, 1876.

19. Adler, A.: Ueber den Druck in der Harnblase zugleich ein Beitrag zur Funktion des Blasenmechanismus, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **30**:487, 1918.

20. Hirsch, E. W.: Relation of Bladder Pressure to Bladder Function, J. A. M. A. **91**:772 (Sept. 15) 1928.

21. Schwarz, O., and Brenner, A.: Untersuchungen ueber die Physiologie und Pathologie der Blasenfunktion, Ztschr. f. urol. Chir. **8**:32, 1921.

22. Rose, D. K.: Clinical Application of Bladder Physiology, J. Urol. **26**:91, 1931.

Foulds [23]). Intermediate values are: 28.5 cm. (Campbell,[24] average of 11 cases) and from 26 to 39 cm. (Pilcher [25]).

From these data it is clear that either the upper or the lower portion of the urinary tract can easily generate a pressure sufficiently high to interfere seriously with its own venous, and at times arterial, circulation.

Starling [26] stated that the pressure in the radial artery (comparable in size to the vesical artery) averages 85 mm. of mercury (114 cm. of water); the venous tension in vessels of comparable size is 9 mm. of mercury (12 cm. of water) or less. The danger of even moderate rises in pressure within the bladder, especially if prolonged, is therefore obvious.

Various means have been used to study the effect of rapid artificial filling of the bladder on both its own activity and that of the upper urinary tract.

The most striking feature of the response of the bladder to distention is its tendency to maintain, within wide limits of filling, a constant pressure, a fact which has been emphasized by Mosso and Pellacani,[27] Sherrington,[28] Rose [22] and others. The level of this pressure appears to be rather constant, but varies with certain extraneous influences (Mosso and Pellacani,[26] Hirsch [20] and Boeminghaus [29]), such as temperature and psychic stimuli. It ranges between 6 and 12 cm. of water. When distention is carried past the capacity of the bladder to relax, very high pressures may result. Goltz [30] observed rhythmic contractions of the wall of the bladder during filling. Rose [22] and others noted that once the bladder has been filled and emptied immediate refilling with a similar quantity of fluid provokes a sharper reaction than does the first injection.

Hitherto it has generally been believed that high pressures in the bladder develop as a consequence of the muscular activity of its own

23. Bumpus, H. C., Jr., and Foulds, G. S.: Gradual Emptying of the Overdistended Bladder, J. A. M. A. **81**:821 (Sept. 8) 1923.

24. Campbell, M. F.: Studies in Bladder Decompression, J. Urol. **17**:371, 1927.

25. Pilcher, P. M.: Prostatectomy in Two Stages, Ann. Surg. **59**:500, 1914.

26. Starling, E. H.: Principles of Physiology, ed. 5, Philadelphia, Lea & Febiger, 1930, p. 763.

27. Mosso, A., and Pellacani, P.: Sur les fonctions de la vessie, Arch. ital. de biol. **1**:97 and 291, 1882.

28. Sherrington, C. S.: Postural Activity of Muscle and Nerve: II. Visceral Muscle, Brain **38**:213, 1915.

29. Boeminghaus, H.: Zur Feststellung des Einflusses der Blasenfüllung auf die Funktion der Nieren, Deutsche med. Wchnschr. **51**:138, 1925; Ueber funktionelle Zusammenhänge zwischen Harnblase und Niere (vesico-renaler Reflex), Arch. f. klin. Chir. **154**:114, 1929.

30. Goltz, F.: Ueber die Funktionen des Lendenmarks des Hundes, Arch. f. d. ges. Physiol. **8**:460, 1874.

wall. However, as I have shown, the detrusor urinae of the dog is normally incapable of exerting pressures of more than 30 to 40 cm. of water (from 22 to 29 mm. of mercury) on stimulation, and pressures above this level result from contraction of the abdominal wall and the diaphragm, i. e., attempts to void. True, high pressures can be produced in the exposed bladder, which is thus free from the influence of voluntary muscular contraction, but in this case they represent not the activity of the bladder but an external force (the pressure of the fluid injected) exerted against the wall of a bladder distended to such a degree that it can relax no further.

When distention sufficient to raise the intravesical pressure is employed, ureteral peristalsis is altered. Sampson [31] studied the excised fresh urinary tract of the dog and found that filling the bladder caused an increase in the frequency and a diminution in the amplitude of the peristaltic waves.

Lucas [5] traced ureteral peristalsis in the dog under morphine by means of a T-cannula and kymograph; an increase in intravesical tension caused also a quickening of ureteral peristalsis with a diminution in its amplitude. Israel [32] obtained similar results in etherized dogs. Pico [33] and Sérès [34] observed peristalsis in the exposed ureter and measured the outflow from its cut proximal end during distention of the bladder; they found it increased in the anesthetized dog. Graves and Davidoff [35] and Wislocki and O'Conor [36] found peristalsis in the exposed ureter of the anesthetized rabbit increased by vesical distention.

Pflaumer [37] watched with the cystoscope the jets of urine which escaped from the ureteral meatus of the unanesthetized dog and found

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31. Sampson, J. A.: Ascending Renal Infection with Especial Reference to the Reflux of Urine from the Bladder into the Ureters, Bull. Johns Hopkins Hosp. **14**:334, 1903.

32. Israel, W.: Das Verhalten der Nieren- und Harnleiter-Tätigkeit während der Blasenkontraktion, Ztschr. f. Urol. **21**:614, 1924; Harnleitermündung und Blasenkontraktion, Klin. Wchnschr. **5**:1878, 1926.

33. Pico, O. M.: Réflexe vesico-rénal, Compt. rend. Soc. de biol. **83**:1499, 1920.

34. Sérès, M.: Corrélation fonctionelle vésicorénale, J. d'urol. **16**:177, 1923.

35. Graves, R. C., and Davidoff, L. M.: Studies on the Ureter and Bladder with Especial Reference to Regurgitation of the Vesical Contents, J. Urol. **10**:185, 1923; Studies on the Ureter and Bladder with Especial Reference to Regurgitation of the Vesical Contents, ibid. **12**:93, 1924; Studies on the Ureter and Bladder with Especial Reference to Regurgitation of Vesical Contents; Regurgitation as Observed in Cats and Dogs, ibid. **14**:1, 1925. Graves, R. C.: Studies on the Ureter and Bladder with Especial Reference to Regurgitation of the Vesical Contents: Bladder Pressure-Curve in the Human, ibid. **18**:321, 1927.

36. Wislocki, G. B., and O'Conor, V. J.: Experimental Observations upon the Ureters, with Especial Reference to Peristalsis and Antiperistalsis, Bull. Johns Hopkins Hosp. **31**:197, 1920.

37. Pflaumer, E.: Cystoskopische Beobachtungen zur Physiologie der Harnleiter und Nieren, Ztschr. f. Urol. **13**:367, 1919. Pflaumer, E., and Höcker, H.: Ureterphysiologie und Uroselektan, Deutsche Ztschr. f. Chir. **229**:309, 1930.

that increased intravesical pressure led to a diminution in their frequency and volume, an observation which was verified by Schmidt [38] in man. These investigators attributed the change to compression of the intramural ureter.

Kreutzmann,[17] using a catheter passed through the cystoscope, found that a rise in the pressure in the bladder increased tension in the ureter in man, but did not exclude the possibility of regurgitation of the contents of the bladder alongside the catheter.

A perusal of what has been written about the possibility of regurgitation of the bladder urine into the ureters during vesical distention is apt to be confusing. Semblinow,[39] Lewin and Goldschmidt,[40] Courtade and Guyon,[41] Markus,[42] Wislocki and O'Conor,[30] von Lichtenberg [43] and Graves and Davidoff [35] all observed such regurgitation into the ureter of the anesthetized rabbit. On the other hand, Sampson,[21] Lucas,[5] Draper and Braasch [44] and Bush and McCradie [45] were unable to produce it in the dog. Satani [46] denied its occurrence in the pig. Eisendrath,[47] Schmidt,[38] Kelly,[48] Young,[49] Bumpus [49a] and others do not believe

38. Schmidt, A.: Die Insuffizienz der vesikalen Harnleitermündung und der Funktionszustand der Harnleitermuskulatur, Beitr. z. klin. Chir. **141**:50, 1927.

39. Semblinow: Zur Pathologie der durch Bakterien bewirkten aufsteigenden Nephritis, Inaug. Dissert., 1885.

40. Lewin, L., and Goldschmidt, H.: Die Resorption körperfremder Stoffe aus der Harnblase, Arch. f. exper. Path. u. Pharmakol. **37**:60, 1896.

41. Courtade, D., and Guyon, J. F.: Sur le reflux du contenu vésical dans les urétères, Compt. rend. Soc. de biol. **46**:556, 1894.

42. Markus, H.: Experimentelle Untersuchung ueber das Rückströmem von Blaseninhalt, Wien. klin. Wchnschr. **16**:725, 1908.

43. von Lichtenberg, A.: Ueber den Begriff "Hydronephrose" in allgemeinen und ueber den Nachweis der durch akzessorische Gefässe verursachten "Hydronephrose" mit der Roentgenuntersuchung, Ztschr. f. Urol. **18**:585, 1924.

44. Draper, J. W., and Braasch, W. F.: The Function of the Ureterovesical Valve, J. A. M. A. **60**:20 (Jan. 4) 1913.

45. Bush, A. D., and McCradie, R. S.: Competency of the Ureterovesical Valves, Am. J. Physiol. **68**:107, 1924.

46. Satani, Y.: Experimental Studies on the Ureter, Am. J. Physiol. **49**:474, 1919; ibid. **50**:342, 1919.

47. Eisendrath, D. N.; Katz, H., and Glasser, J. M.: Bladder Reflux; Clinical and Experimental Study, J. A. M. A. **85**:1121 (Oct. 10) 1925.

48. Kelly, H. A.: The Reflux of Air into the Ureters Through the Air-Distended Bladder in the Knee-Breast Posture, Am. J. Obst. **40**:468, 1879.

49. Young, H. H.: Hydraulic Pressure in Genitourinary Practice, Especially in Contracture of the Bladder, Bull. Johns Hopkins Hosp. **9**:100, 1898; Practice of Urology, Philadelphia, W. B. Saunders Company, 1926, vol. 1, p. 17.

49a. Bumpus, H. C.: Urinary Reflux, J. Urol. **12**:341, 1924.

that it occurs normally in man, while Kretschmer [50] and Graves [51] observed it (contrast medium under the fluoroscope) in apparently normal persons.

Sampson's [31] original description of the ureterovesical valve did much to clarify the situation, but the most adequate explanation of the confusion is that of Gruber,[52] who pointed out that the ureter of the dog and pig and of man enters the bladder obliquely and is guarded by a thick, well developed valve, while that of the rabbit passes through the wall of the bladder almost at right angles and possesses little or nothing in the way of a valve. He was able to produce reflux in the dog only after injuring the valve. De la Pena [53] obtained similar results from dividing the fibers of the detrusor urinae from without in the area where they overlie the intramural ureter, thus affirming the importance of both the valve and the oblique course of the ureter in preventing reflux. The clinical importance of these factors has been emphasized by Young,[49] Kelly,[48] Warschauer,[54] Alksne,[55] Eisendrath,[47] Satani,[46] Bumpus, Caulk [56] and others.

To summarize, during filling of the bladder, high pressures may develop. When these pressures exceed from 30 to 40 cm. of water, the excess is apparently due either to distention of the organ to such a degree that it can no longer relax or to contraction of the abdominal muscles and the diaphragm. When the intravesical tension rises above 6 to 12 cm. of water, the rate of ureteral peristalsis is increased, while its amplitude is diminished. In spite of the increased rate of peristalsis in the ureter, the frequency with which jets of urine are ejected into the bladder is diminished. This seeming discrepancy is probably to be explained by the fact that most observers have selected one area in the ureter for observation and have not considered the fact that the rate in the vesical end of the ureter is normally lower than that elsewhere (Boulet [57]).

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50. Kretschmer, H. L.: Cystography, Surg., Gynec. & Obst. **23**:709, 1916.

51. Graves, R. C.: Studies on the Ureter and Bladder with Especial Reference to Regurgitation of the Vesical Contents, Tr. Am. A. Genito-Urin. Surgeons **20**: 98, 1927.

52. Gruber, C. M.: The Function of the Ureterovesical Valve and the Experimental Production of Hydronephrosis, J. Urol. **23**:161, 1930.

53. de la Pena, A.: Personal communication to the author.

54. Warschauer, E.: Beobachtungen aus der Nieren- und Ureteren- Physiologie, Berl. klin. Wchnschr. **38**:398, 1901.

55. Alksne, J.: Ein Beitrag zur normalen und pathologischen Physiologie des Ureters, Folia urol. **1**:338, 1907-1908.

56. Caulk, J. R.: The Significance of the Ureter in Surgery, Surg., Gynec. & Obst. **49**:228, 1929.

57. Boulet, L.: Sur les mouvements de l'urétère humain, Compt. rend. Soc. de biol. **74**:1171, 1913.

Reflux probably does not occur in the ureters of the normal human being or dog because of their oblique course, which leads to compression by the contents of the bladder, and because of the valves which guard them. Exceptions like those of Kretschmer [50] and Graves [51] are best explained by the fact that the ordinary contrast mediums cause sufficient irritation to set up abnormal conditions, so that the regurgitation of such solutions up the ureters or normal human beings is not a "normal" phenomenon (Schmidt [88]).

EXPERIMENTAL STUDY

Normal male dogs were used. Anesthesia was obtained by the subcutaneous injection of 10 mg. of morphine sulphate for each kilogram of body weight, supplemented, if necessary, by infiltration of the abdominal wall with 0.5 per cent procaine hydrochloride without epinephrine hydrochloride. Through an incision in the left rectus abdominis the left ureter was exposed just above the point at which it crossed the iliac vessels. It was not stripped, but the muscularis was

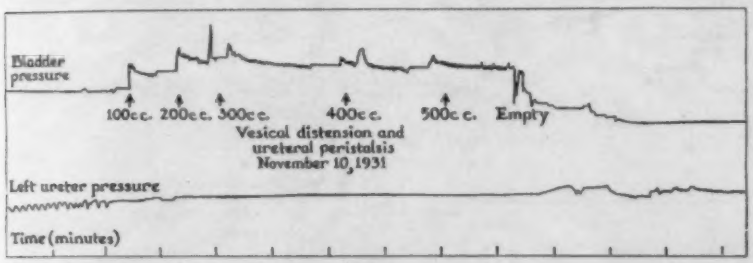

Fig. 1 (experiment 1).—Kymograph tracing showing cessation of ureteral peristalsis on distention of the bladder; peristalsis returned on emptying it.

transfixed by a fine silk traction suture. A short longitudinal incision was made into its lumen just below the suture, and a T-cannula made from a 20 gage steel needle was inserted. The ureteral incision was closed with silk sutures snugly enough to be water-tight. The cannula was connected to a glass tube, which was brought out through a stab wound in the lateral abdominal wall. The tube was stitched to the posterior abdominal wall to prevent kinking of the ureter. The right ureter was divided near the bladder, and the vesical end was cannulated. The renal end was left open. The cannula was connected to a rubber tube which was brought out through the abdominal incision and allowed to drain into a cup.

The glass tube from the left ureter was then connected to a water manometer which recorded on smoked paper in a kymograph. A rubber catheter was passed into the bladder and connected, by means of a T-tube and a three-way valve, to a reservoir of sterile physiologic solution of sodium chloride, colored blue with indigotindisulphonate, U.S.P. (indigocarmine), and kept at body temperature, and to a mercury manometer which also recorded on the smoked paper.

When peristaltic waves appeared, the bladder was distended by injecting 50 cc. of colored sterile saline solution, and the resultant pressure in the bladder and ureter was recorded.

Experiment 1.—In a male dog weighing 12 Kg. peristaltic waves appeared directly the apparatus was set up. When 100 cc. of fluid had been injected into

the bladder, the waves suddenly disappeared (fig. 1). This occurred with an intravesical pressure of 22 mm. of mercury (30 cm. of water). Injection was continued until the bladder contained 500 cc. at a pressure of 100 mm. of mercury. Emptying of the bladder was followed by a return of peristalsis and by a sharp rise of tension. The frequency of peristalsis was increased, but its amplitude was diminished. At no time did indigotindisulphonate appear in the glass tube leading from the left ureter or from the distal stump of the right ureter.

EXPERIMENT 2.—In a male dog weighing 15 Kg. the procedure was carried out as in the foregoing experiment, except that the injections were made in quantities of 100 cc. Peristalsis disappeared at a vesical tension of 26 mm. of mercury. When 500 cc. had been injected (pressure, 122 mm.) the bladder unexpectedly burst (fig. 2). There was a sharp rise of intra-ureteral tension within a few seconds, accompanied by small frequent peristaltic waves. No indigotindisulphonate appeared in the glass tube connected to the ureteral cannula or from the vesical end of the right ureter.

EXPERIMENTS 3 and 4.—These were identical with experiment 1. Peristalsis disappeared when the intravesical tension exceeded 31 mm. of mercury (42 cm. of

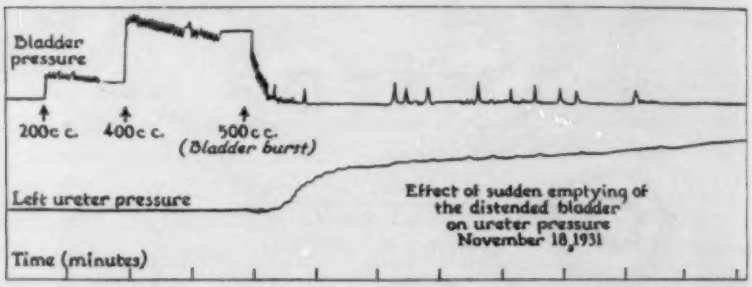

Fig. 2 (experiment 2).—Tracing showing the rise in ureteral tension on bursting of the bladder (photograph when camera is set for figure 1).

water) in experiment 3 and 22 mm. of mercury (29.9 cm. of water) in experiment 4. It returned when the bladder was emptied, always with a definite rise in tension and with increased frequency but diminished amplitude. The blue-stained distending fluid did not appear in the glass arm of the cannula or from the stump of the right ureter.

Comment.—Sudden distention of the bladder to a pressure in excess of 22 mm. of mercury (30 cm. of water) caused abrupt cessation of peristalsis in the ureter. Release of the intravesical tension caused a return of peristalsis, with a slight rise of tension. An inquiry into the mechanism which stopped peristalsis seemed in order.

EXPERIMENTS 5 and 6.—It was suspected that powerful contraction of the wall of the bladder as a result of the strong stimulation of rapid distention was involved. In these experiments the procedure was the same as in the preceding four, except that, following cannulation of the ureter, the lower end of the incision in the abdomen was left open and the bladder was allowed to protrude so that it could be observed.

When the bladder was distended, in neither case was there any significant change in the rate or the amplitude of the peristalsis (fig. 3). There was a slight fall in pressure, which returned to its previous level when the bladder was emptied.

It is to be noted that the curve of the pressure in the bladder was much different from that in the previous experiments, being much flatter; the maximum reading was lower, and respiratory variations were absent.

The wall of the bladder was stimulated electrically while the bladder was empty and again while it contained a small amount of fluid. Although the pressure rose to between 20 and 25 mm. of mercury (from 27 to 34 cm. of water), no cessation of peristalsis occurred. No blue fluid appeared in the arm of the cannula or in the abdomen.

Comment.—Apparently the cessation of peristalsis which accompanied vesical distention did not depend on contraction of the wall of the bladder.

In order to test whether this cessation of peristalsis was a reflex excited by stretching of the wall of the bladder, the last two animals were again used in experiments 6 and 7.

EXPERIMENTS 7 and 8.—A sterile, inelastic cloth bag having a capacity of 150 cc. was slipped over the bladder, which was allowed to protrude from the open incision. Distention of the bladder still failed to influence the ureteral peristalsis, although the pressure was raised to 200 mm. of mercury (272 cm. of

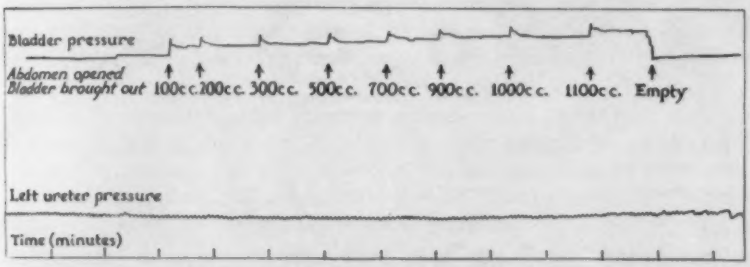

Fig. 3 (experiment 5).—Tracing showing that peristalsis was not influenced by distention of the bladder while it protruded from an abdominal incision.

water), a procedure which caused multiple hemorrhages in the wall of the bladder. No blue fluid appeared in the side arm of the ureteral cannula or from the right side.

Comment.—Apparently this phenomenon was independent of the absolute tension in the bladder, but depended on some other factor. Since it had been noted that the bladder of the dog, when rapidly distended, always produced bulging of the abdominal wall, even when the fluid content was small, it was suspected that the cessation of peristalsis might depend on a reflex excited when the full bladder impinged on the abdominal wall.

EXPERIMENTS 9 and 10.—The animals used in these experiments were normal males weighing 9 and 11 Kg., respectively. Distention of the bladder caused disappearance of peristalsis when pressures of 22 and 24 mm. of mercury (30 and 32 cm. of water), respectively, were reached. The cloth bag already described was slipped onto the bladder, and the abdomen was closed. When the tension in the bladder reached the previous level, the lower part of the abdominal wall could be seen to bulge; peristalsis ceased. Emptying the bladder resulted in a return of peristalsis, accompanied by a rise of pressure in the ureter.

The abdomen was reopened. While the bladder was empty, traction was made with the finger on the peritoneum at the edge of the abdominal incision. Peri-

stalsis ceased, but returned when traction was abandoned. The usual slight rise of pressure accompanied the return of peristalsis. At no time did blue fluid appear in the arm of the ureteral cannula or in the abdomen.

Comment.—It seemed safe to conclude that the cessation of peristalsis which accompanied vesical distention was due to a reflex excited by compression or stretching of the portion of the abdominal wall which was compressed by the distended bladder.

It had been noted that, although urine appeared to flow from the ureter into the bladder in all experiments until the vesical distention stopped peristalsis of the ureter, the recorded pressure in the bladder always exceeded that in the ureter. In order to investigate this apparent paradox, experiments 11 and 12 were performed.

EXPERIMENT 11.—In a male dog weighing 13 Kg. the right ureter was cut, and the vesical end was tied. The left ureter was cannulated in the usual fashion,

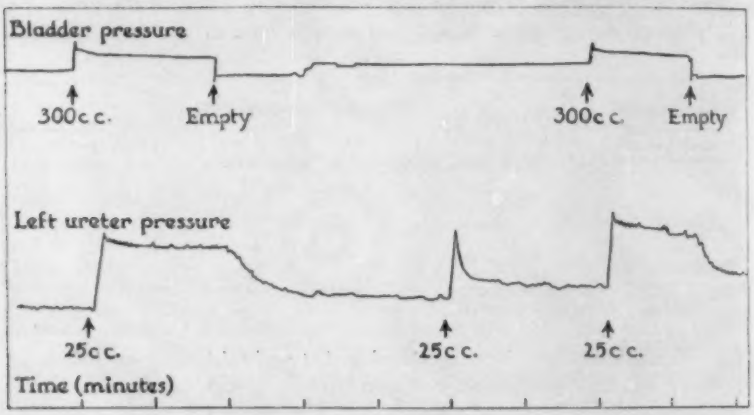

Fig. 4 (experiment 11).—Tracing showing how the pressure developed in the ureter by the injection of saline solution fell with the development of peristalsis (photograph when camera is set for figure 1).

but clear saline solution was used to fill the bladder and indigotindisulphonate was given intravenously to color the urine which came down the ureters.

When 200 cc. of fluid had been injected into the bladder, the tension was 23 mm. of mercury (31 cm. of water), while the ureteral pressure was only 4.7 mm. of mercury (6.4 cm. of water). Yet when the fluid from the bladder was withdrawn, it was blue from the first, indicating that urine had been passing into the bladder.

A small amount (25 cc.) of sterile saline solution was then injected slowly into the ureteral cannula. A prompt rise of pressure resulted (fig. 4). Peristalsis increased in amplitude, and a slight fall in the tension in the ureter occurred. When the bladder was emptied, the pressure fell rapidly, but not to the base line. A second injection into the ureter resulted in a sharp rise in pressure, which fell almost at once. Refilling of the bladder was followed by injection of the ureter. The ureteral pressure now fell very slowly until the bladder was emptied, when it dropped rapidly. At no time did the pressure in the ureter equal that in the bladder, even though urine could be shown to be passing into the bladder.

EXPERIMENT 12.—This was a repetition of the foregoing experiment, except that no indigotindisulphonate was given intravenously, but was injected into the ureter instead. It stained the fluid of the bladder while the tension in the ureter was below that in the bladder. Injection into the ureter was followed by a rapid fall of pressure in the ureter if the bladder was empty and by a slow decline if it was distended. Only when the bladder was empty did the pressure in the ureter exceed that in the bladder. Yet blue-stained irrigating fluid appeared in the bladder, even when it was distended.

Comment.—The apparent paradox of water passing from an area of low to one of higher pressure is explicable only on the basis of the functional ability of the ureter. As Lucas [6] demonstrated, the isolated ureter of the dog can sustain a pressure of 92 cm. of water. It is easy to see, therefore, how the segment of the ureter between the cannula and the bladder can generate sufficient pressure to force the urine into the bladder. The cannula was at the level of the iliac vessels so that an inch or more of ureter was available for creating the necessary force.

It is to be noted that thus far no reflux of the stained contents of the bladder had occurred, either into the glass arm of the cannula or into the vesical stump of the right ureter.

After the determination of what happens when the bladder is distended rapidly, a standard thereby having been set up, it seemed desirable to determine whether acute urinary retention altered the response of the bladder or ureter to distention of the former.

Method.—Normal male dogs excreting normal, sterile urine were used. The urethra was ligated in the perineum with linen tape under local anesthesia, and with sterile precautions. The animals were placed in cages designed for measuring the metabolism to permit one to be certain that no urine escaped. After retention had been established, the investigations already described were repeated.

EXPERIMENT 13.—A male dog weighing 12 Kg. was used. After twenty-four hour retention, the abdomen was opened under morphine and procaine hydrochloride anesthesia. The bladder was greatly distended and cyanotic. There were no visible hemorrhages in its wall. It was surrounded by warm, moist bowel, and was dislocated through the incision. A rubber-shod clamp was placed upon the left ureter just above the iliac vessels; the ureter was cannulated and connected to the water manometer. The vesical end of the right ureter was cannulated. The abdomen was closed, with the handles of the rubber-clad clamp protruding. The urethral ligature was removed, and a rubber catheter was passed into the bladder and tied. It was at once connected to the mercury manometer, without the loss of urine. The clamp was then removed from the ureter.

The pressure in the bladder was 8 mm. of mercury (10.9 cm. of water); distention of the bladder produced, at a tension of 21 mm. of mercury (28.0 cm. of water), abrupt cessation of peristalsis; on emptying the bladder peristalsis returned, with a definite rise of pressure. These changes could be reproduced at will.

At no time did the irrigating fluid appear in the side arm of the T-cannula or from the vesical stump of the right ureter.

EXPERIMENT 14.—A dog weighing 20 Kg. was used. After urinary retention of forty-eight hours' duration the bladder was hugely distended and was cyanotic, with hemorrhages in the posterior wall. Connection of the left ureter and the bladder to manometers was accomplished without loss of fluid. Tracing of peristalsis began at once. The pressure was 12 cm. of water (fig. 5). The bladder was flaccid. One hundred cubic centimeters of blue irrigating fluid was injected. The pressure in the ureter had been rising gradually before the injection and

continued to do so. Some diminution in the peristaltic rate was noted. The withdrawal of 70, then 50, cc. of urine caused a slight fall in ureteral tension. The bladder was emptied suddenly. The pressure in the ureter fell to zero; the peristalsis increased in rate, but its amplitude diminished. No reflux was observed. The animal was killed for anatomic studies.

EXPERIMENT 15.—This experiment was a duplicate of the preceding one. The bladder was distended and cyanotic and showed hemorrhages in the posterior wall. When manometers were connected, the pressure in the bladder and that in the ureter were 20 and 17.4 cm. of water, respectively. On the addition of 200 cc.

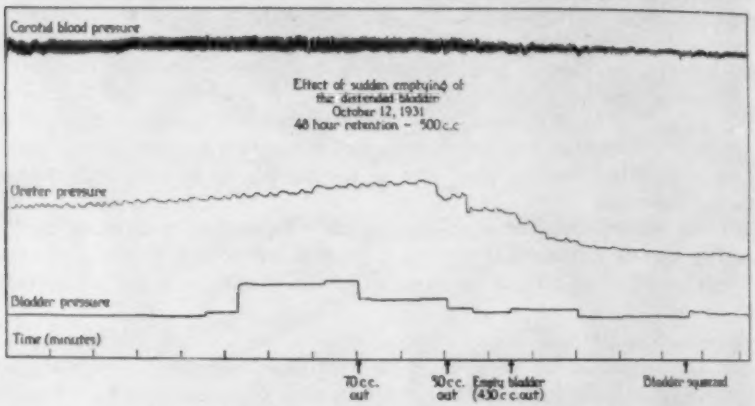

Fig. 5 (experiment 14).—Effect of sudden emptying of the distended bladder (500 cc.) after forty-eight hour retention on ureteral peristalsis.

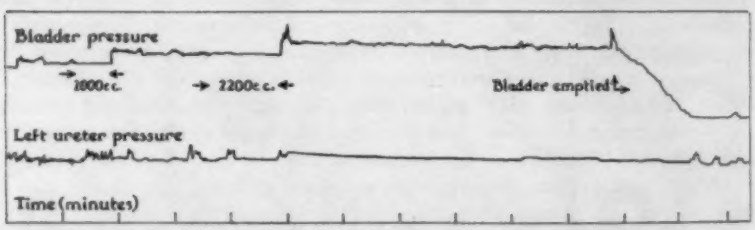

Fig. 6 (experiment 15).—Tracing showing cessation of ureteral peristalsis on further filling of a bladder already obstructed for forty-eight hours; peristalsis returned on emptying the bladder.

of blue irrigating fluid to the contents of the bladder, the peristalsis of the ureter diminished in frequency. On the injection of another 200 cc. it ceased. Withdrawal of the contents of the bladder (2,200 cc.) was followed by a return of peristalsis of a very low frequency (fig. 6). There was no rise in pressure.

No regurgitation up either ureter could be detected.

EXPERIMENT 16.—A male dog weighing 18 Kg. was used. The experiment was a duplicate of experiment 14, except that the retention was maintained for seventy hours. The bladder was enormously distended and was hemorrhagic and gangrenous. The tension in the bladder was 8 cm. of water, and in the ureter

4 cm. Peristalsis was active. It was inhibited by the injection of fluid into the bladder and reappeared, without a rise of pressure, on emptying the bladder. No regurgitation of fluid up either ureter could be seen.

Comment.—The mechanism causing inhibition of ureteral peristalsis during sudden rises of the intravesical tension persists for as long as seventy hours after the development of urinary retention. Experiments were discontinued at that time because previous work had shown that the bladder invariably ruptures at about seventy hours. The persistence of this mechanism after the extreme disorganization of the wall of the bladder in seventy hour retention fortifies the initial view that the reflex depends on some extravesical mechanism.

GENERAL COMMENT

If the statements in the literature are true, water can run uphill, in so far as it appears to pass from an area of negative pressure (the renal pelvis) to an area of positive pressure (the urinary bladder). To accomplish this feat, nature has evolved an ingenious mechanism and has taken many precautions to protect the kidney against regurgitation of urine from the bladder.

As has been pointed out, the pressure in the pelvis is usually negative. As peristalsis drives the urine down the ureter, its pressure rises until it is positive by a few centimeters of water in the vesical end of the ureter. From here the urine passes into an active muscular reservoir, where the average tension is about from 6 to 10 cm. of water. The activity of this reservoir has been admirably gaged to prevent the too frequent development of high pressures and consequent damage, by permitting it to maintain a constant degree of pressure within wide limits of filling—the postural tone of Sherrington.[28]

To prevent the retrograde propagation of the pressure of the bladder a fourfold mechanism exists. The first factor, the ureterovesical valve of Sampson,[31] closes off the ureteral meatus mechanically when the vesical tension rises. This is supplemented by a second mechanism, the oblique course of the ureter in the wall of the bladder (Israel [32]). This arrangement is such that contraction of the detrusor urinae constricts the ureter, an effect which is augmented by the anteroposterior compression resulting from the intravesical tension. A third factor has received little emphasis but is probably equal in importance to the first two, namely, ureteral peristalsis. Pflaumer [37] and others have shown by means of intravenous urography that the normal ureter is probably never entirely filled throughout its length, but is divided into segments by peristaltic contractions. As has been already pointed out, the individual peristaltic wave may, on occasion, generate a very high pressure (71 mm. of mercury, or 96.5 cm. of water) and may resist a distending pressure of 92 cm. of water. Thus, it would appear that this mechanism alone would suffice to prevent the regurgitation of urine from the bladder to the kidney, except during prolonged and powerful straining.

This ability of the ureter to produce high pressures explains the apparent discrepancy between the tension in the pelvis and ureter and that in the bladder. It is apparent that a short segment of the ureter can generate a high tension without causing any rise a short distance above it. This is the only basis on which one can account for the observations in experiments 11 and 12, in which, in spite of the fact that the intravesical tension exceeded that in the ureter during the whole period of observation, urine flowed into the bladder. It is undoubtedly this mechanism which prevents dilatation of the ureter and renal pelvis during the early stages of chronic urinary retention.

The efficiency of these mechanisms is great, if one may judge from the literature. The fact that urinary reflux is almost never observed in the normal dog or human being, while occurring with great regularity in the rabbit, emphasizes, as Gruber [52] has shown, the importance of the oblique course of the intramural ureter.

The results of this series of experiments corroborate the view that reflux is rare in the dog, since it was never observed either during rapid distention or stimulation of the normal bladder (experiments 1 to 10) or during rapid distention or stimulation of the bladder after complete retention lasting as long as seventy-two hours.

A fourth protective mechanism, which has apparently not been described previously, was demonstrated by the foregoing series of experiments, namely, a reflex which stops ureteral peristalsis when the intravesical tension rises suddenly (experiments 1 to 4, 7 to 10 and 13 to 16). A need for this reflex exists. While the backward transmission of pressure in the normal urinary tract is effectively prevented, a dangerous situation might nevertheless develop if a high vesical tension were present for any length of time, owing to the ability of the kidney and ureters to produce pressures as high as 70 mm. of mercury (95 cm. of water). It is clear that if a high vesical tension persisted the upper urinary tract would build up a tension sufficient to interfere with its own venous return and thus to cause serious lesions. It is undoubtedly this mechanism which produces the renal and ureteral hemorrhages in experimental acute retention as well as those occurring after ligature of the ureter.

That it is a reflex which arises outside the wall of the bladder is shown clearly by experiments 5 and 6, in which ureteral peristalsis persisted in spite of electrical stimulation of the wall of the bladder, and by experiments 14 to 16, in which peristalsis stopped on distention when the bladder was so badly damaged by retention that it could not contract spontaneously. Experiments 7 to 10 prove that stretching of the wall of the bladder, with the resultant stimulation of the vesical nerves, plays no part in its production.

Its dependence on the nerves of the abdominal wall was first suggested by the visible forward bulging of the bladder during distention of sufficient degree to arrest ureteral activity. This view is verified by experiments 5 to 8, in which bringing the bladder out of the abdomen, while it failed to alter ureteral peristalsis, did prevent its arrest by vesical distention, and by experiments 9 and 10, in which the reflex was excited by traction on the parietal peritoneum.

The period during which this reflex protects the upper portion of the urinary tract has not been determined accurately, but in experiments 13 to 16 and during a long series of experimental acute retentions previously reported[58] it was found that the kidneys and ureters remained normal for twenty-four hours invariably, and for forty-eight hours in some instances, after urethral ligature. From this it may be inferred that the mechanism fails at some time between twenty-four and forty-eight hours after the onset of retention. Further evidence of its efficiency is obtained from the rapidity with which renal lesions develop after ligature of the ureter. Fabian [8] found edema of the peripelvic fat fifteen minutes after ligature of the upper ureter and hemorrhage within three hours. Helmholz and Field [10] ligated the ureter lower in the rabbit and observed edema within four, and hemorrhages within eighteen, hours.

It is my belief, as yet not proved, that the damage in acute retention is due not to sustained high pressure but to the intermittent attempts to void, which may produce remarkable rises in intravesical tension, a supposition which would explain why this reflex may persist so long and prove to be so effective.

SUMMARY AND CONCLUSIONS

1. The literature on pressure relations in the urinary tract has been reviewed. The fact that intravesical tension is usually higher than the pressure in the renal pelvis and that the maximum pressure attainable by the bladder exceeds that attainable by the renal pelvis and ureter combined necessitates some mechanism to protect the kidney against the bladder.

2. The literature describes a threefold mechanism for this purpose, consisting of the ureterovesical valve of Sampson, the oblique course of the ureter through the wall of the bladder and the peristaltic contractions of the ureter. The last-mentioned factor is probably more important than one would suspect from the literature, since a short segment of the ureter can develop a pressure of 90 cm. of water and can resist a similar distending pressure.

58. Creevy, C. D.: Distention of the Urinary Bladder: I. Hematuria and Sudden Emptying; Experimental and Clinical Study, Arch. Surg. **28**:948 (May) 1934.

3. A series of 16 experiments on the dog has revealed the existence of a fourth protective mechanism, a reflex which stops ureteral peristalsis during periods of sudden increase in the intravesical tension.

4. This reflex is excited not through the nerves of the bladder but through stimulation of the anterior abdominal wall by the bulging forward of the distended bladder. It persists even when the bladder is badly damaged by intramural hemorrhage.

5. Back pressure probably does not exist in the normal urinary tract of the dog, since the reflux of urine does not occur during sudden distention of the bladder, even after long-standing acute retention. Instead, the injurious pressure is generated by the kidneys and ureters in an attempt to force urine into a distended bladder.

6. The purpose of the reflex seems to be to protect the upper portion of the urinary tract against its own rise in tension during sudden sharp rises in intravesical pressure.

7. The reflex is evidently successful for periods of from twenty-four to forty-eight hours, since the kidneys and ureters remain normal up to that time during acute retention of the urine.

III. BACTERIOPHAGES IN TREATMENT OF COLON BACILLUS SEPTICEMIA

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Septicemia due to the colon bacillus, though less common than septicemia due to the cocci, is ordinarily a disease of high mortality. It arises as a terminal phase of an ascending urinary infection and less frequently by extension of septic infection from other regions of the body. During the past three years we have seen and treated three patients with this condition and have had the opportunity to furnish bacteriophage preparations and advice as to their application for two other patients.

The cooperation of the patient, the clinician and the bacteriologist in this small group has presented a sharp contrast when compared with that experienced with the larger group of patients with urologic diseases. The patient with septicemia is usually in sufficient distress that he and his family are willing to follow the advice of the physician; and after a succession of positive blood cultures coupled with severe chills, sharp spikes of temperature, toxic psychic manifestations and other alarming signs and symptoms have been observed, the clinician is more inclined to welcome any possible aid which may be offered by modern laboratory service. The serious nature of the disorder also challenges the best efforts of the laboratory worker, who senses the enhanced valuation of his own work in relation to these more desperate clinical problems and is thus stimulated to superlative effort.

The records for four of these patients are quite complete, and they will be presented here in summarized form. The fifth patient came under observation during the preparation of this paper, and the record is not yet available for presentation.

REPORT OF CASES

CASE 1.—M. L., a white woman, aged 21, admitted to the hospital on March 16, 1931, has been mentioned in earlier publications from this department, and her case was selected as the example of this group to be used in the more general discussion [1]

These studies have been aided by a grant from the Josiah Macy Jr. Foundation.

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1. MacNeal, Ward J.: Specific Treatment of Septic Infections, Particularly with Aid of Bacteriophages, Am. J. M. Sc. **189**:623, 1934.

of septic infections presented before the Section on Pharmacology and Therapeutics at the meeting of the American Medical Association at Milwaukee, June 16, 1933. It will suffice here to state that she suffered from pelvic thrombophlebitis, following an abortion, with repeated blood cultures positive for the colon bacillus. Following intravenous bacteriophage therapy she made a complete recovery and was discharged in excellent condition on April 28, 1931. This is probably our most striking example of apparent success in the treatment of colon bacillus septicemia with bacteriophage.

Case 2.—G. J., a white woman, aged 43, suffered from an infection in her right foot from June 15 to June 25, 1932. As this was healing she began to have chills and fever, with a rise of temperature to 105 F. A blood culture taken on June 25 and brought to our laboratory gave abundant growth of colon bacilli, variety communis, in two flasks of broth and in three agar plates. A diagnosis of pyelitis was made, and after treatment with methenamine for ten days she was much improved. However, on July 21 she fell in a faint while walking toward the door of her room, and from that time she was weak and dizzy. On July 26 and 27 she had auditory and visual hallucinations, and on July 28 there was increasing drowsiness until she was admitted to the hospital in a comatose condition at 9: 15 p. m., July 28.

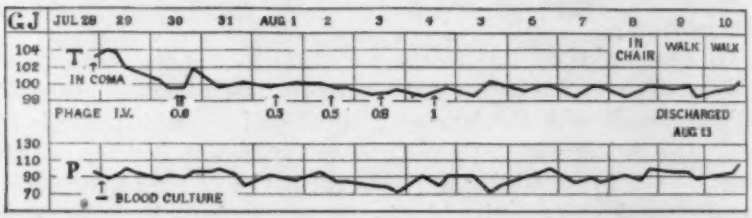

Chart 1 (case 2).—Abridged clinical chart for G. J., showing the course of the temperature (*T*) and pulse rate (*P*), together with outstanding features of the clinical record.

At this time the clinical diagnosis was bacteremia and probable septic thrombosis of the brain.

The clinical course in the hospital is indicated in chart 1. A blood culture taken at midnight on the day of admission remained sterile; a catheterized specimen of urine revealed red blood cells and pus; the blood chemistry and the spinal fluid were normal. Gastric lavage was done, and an infusion of 1,850 cc. of 5 per cent dextrose was given intravenously before 2 a. m. The patient remained unconscious and incontinent throughout the night. During the next day, July 29, she received 1,450 cc. of saline solution subcutaneously. She remained incontinent and unresponsive. On July 30 she became more alert and occasionally conversed in a rational manner. Most of the time, however, she was disoriented, sometimes being very noisy, and she required constant physical restraint in bed. A clysis of 1,000 cc. was given just before noon.

On this day bacteriophage treatment was urgently requested by the patient's physician, who regarded the prognosis as grave. In regard to bacteriology, we had only the evidence seen in a fresh specimen of urine in addition to the positive blood culture obtained on June 25, before the patient's admission to the hospital. However, the chemical analysis of the blood, which had been repeated, disclosed nothing to explain the mental derangement, and it was decided that the possibility of benefit overbalanced the dangers. Therefore, to obtain prompt effect,

the stock asparagine preparation of colon bacteriophage was given intravenously, 1 cc. of a 1:10 dilution at 1:45 p. m.; a second dose of 2 cc. at 2:37 p. m. and a third dose of 3 cc. at 3:18 p. m., on July 30. There was no chill following these injections, and only a moderate rise in temperature to 102 F. at 8 p. m. The next day she was rational but not cooperative. The day being Sunday, one of the physicians had told her that she would not receive any intravenous injections, and when we arrived at the hospital to give her a treatment she emphatically refused to permit it. However, on Monday and the following days she readily submitted to the intravenous therapy, which was discontinued as no longer required after August 4. Intravesical bacteriophage treatment was advised but was refused by the patient, who insisted that she was well enough to go home. A culture of the urine on August 2 yielded 23,000,000 colonies of colon bacilli per cubic centimeter. The organism was a colon bacillus of the communis variety and only partially susceptible to the stock bacteriophage. Without further bacteriophage treatment the patient left the hospital on August 13 and was advised to continue taking methenamine. She came to the laboratory after about a month to inquire about obtaining bacteriophage for further treatment at home and was advised to be admitted again to the hospital for a thorough course of treatment of the

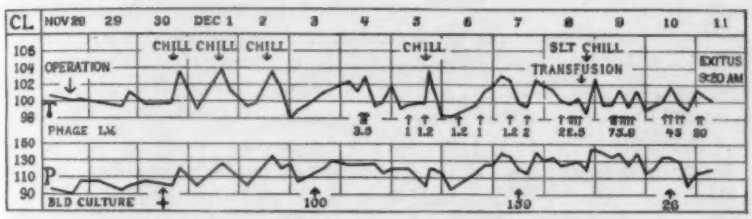

Chart 2 (case 3).—Abridged clinical chart for C. L.

persisting urinary infection. This she declined to do because she did not feel ill enough to make such a sacrifice.

As an example of successful bacteriophage therapy this case is not very satisfactory. The positive blood culture of June 25 contained the same type of colon bacillus found in the urine after the patient's admission to the hospital more than a month later. During the interval the patient had been up and about for part of the time. When admitted to the hospital on July 28 she seemed to be in a dying condition, but the blood culture taken at this time remained negative. Her clinical condition progressively improved, and during part of this period of improvement the colon bacteriophage was injected intravenously. She as well as her physicians ascribed the improvement in large measure to the use of the bacteriophage. One may justly be skeptical about the relationship. Because of lack of cooperation by the patient it was impossible to carry out thorough treatment of the infection of the urinary tract.

Case 3.—C. L., a man, aged 66, had been under treatment for long-standing osteomyelitis of the legs and chronic septic inflammation of the knee joint which had been incised in 1917. On Nov. 28, 1932, a suprapubic prostatectomy was performed. His subsequent clinical record is summarized in chart 2. Following this operation septic fever developed, and the blood culture taken on November 30 yielded colon bacilli. On December 2 the patient was dyspneic. The area of cardiac dulness was enlarged, and there were occasional premature beats. The

blood pressure was 120 systolic and 57 diastolic, and the pulse rate varied from 100 to 135. Coarse râles, squeaks and rhonchi were heard over both lungs, and the squeaks were much diminished after injection of epinephrine. There was evidence of marked arteriosclerosis. A second blood culture taken on December 3 yielded about 100 colonies per cubic centimeter. Bacteriophage therapy was requested on December 4 and promptly initiated by an intravenous injection of 4.3 cc. of a 1:10 dilution of the stock asparagine preparation of colon bacteriophage at 10:04 a. m. This was followed by the administration at 11:12 a. m. of 1 cc. of the undiluted phage intravenously and at 12:13 p. m. of 2.1 cc. of the undiluted phage intravenously. On December 5 he was given an intravenous injection of 1 cc. at 8:15 a. m. and another of 1.2 cc. at 4:05 p. m., which was followed twenty-five minutes later by a chill and a rise of temperature to 103.8 F. at 5 p. m., profuse diaphoresis at 9 p. m. and a drop of temperature to 98.4 F. at midnight. On December 6 he received an intravenous injection of 1.2 cc. of the stock asparagine preparation of bacteriophage at 8:35 a. m. and at 5:10 p. m. 1 cc. of a newly prepared specific bacteriophage in asparagine, representing the filtrate of the lysed bacterial culture isolated from his own blood stream. On December 7 he received 1.2 cc. of the specific phage intravenously at 7:45 a. m. A blood culture was taken at noon, and at 3:55 p. m. another intravenous injection of 2 cc. of the specific bacteriophage was given. On December 8 the many colonies already appearing in the blood culture of the preceding day indicated the futility of the bacteriophage treatment up to that time. Five intravenous injections of the specific bacteriophage were given on this day: 2.5 cc. at 8:05 a. m., 3 cc. at 12:35 p. m., 4 cc. at 1:42 p. m., 5 cc. at 3:06 p. m. and 8 cc. at 4:45 p. m., making 22.5 cc. for the day. He was also given a transfusion of 400 cc. of blood at 5:24 p. m. A slight chill at 8:15 p. m., with a rise of temperature to 102.8 F. at midnight, may have been related to the transfusion or to the bacteriophage or to both. On December 9 the condition was clinically so critical that the dosage of bacteriophage was further increased: 9.7 cc. at 8:15 a. m., 9.1 cc. at 9:35 a. m., 10 cc. at 10:45 a. m., 10 cc. at 12:30 p. m., 15 cc. at 2:58 p. m., 10 cc. at 4:13 p. m. and 12 cc. at 5:34 p. m., making a total of 75.8 cc. for the day. There was no evident chill or significant rise in temperature which could be ascribed to these intravenous injections, and the general condition remained unsatisfactory. There were labored respiration, an irregular pulse and increasing edema of the extremities and trunk. On December 10 he received four intravenous injections of specific bacteriophage: 11 cc. at 9:20 a. m., 12 cc. at 11:55 a. m., 12 cc. at 3:20 p. m. and 10 cc. at 5:20 p. m., making a total of 45 cc. for the day. Through some misunderstanding the subsequent prescribed doses were omitted until after midnight. Two doses of 10 cc. each were then given, one at 1 a. m. and the next at 3 a. m. Respiration ceased at 9:14 a. m. The blood culture taken at 11:45 a. m. on December 10 yielded 26 colonies per cubic centimeter of blood, and the bacteriophage was recovered from the broth of this blood culture.

Case 4.—A. C. T., a white woman, aged 25, was admitted to the service of Dr. Eugene Dalton at the Methodist Episcopal Hospital in Brooklyn on Dec. 31, 1932. We are indebted to the house physician, Dr. Hugh K. Miller, for the records. The patient, married in July 1932, was at the end of the fourth month of her first pregnancy, which had been free from disturbances except for morning sickness on one day in October, incontinence of urine since July and frequency of micturition since August, with nocturia, the patient urinating three or four times each night, up to December 26. On this day she began to have headache and severe vomiting, which became continuous. On December 29 she began to cough. Examination of the urine before admission revealed pus cells. On admis-

sion (December 31) the temperature was 104 F., the pulse rate 120 and the respiratory rate 36; the abdomen was enlarged, and the uterine fundus extended 130 mm. above the symphysis; there were marked tenderness in the left flank and slight pharyngitis. The urine on Jan. 1, 1933, revealed leukocytes and erythrocytes. The blood count showed 15,500 white cells with 91 per cent polymorphonuclears. Vomiting, which had persisted up to this time, ceased on January 2. A blood culture taken on January 3 revealed colon bacilli, and another blood culture taken on January 5 showed abundant colon bacilli the next day. A transfusion

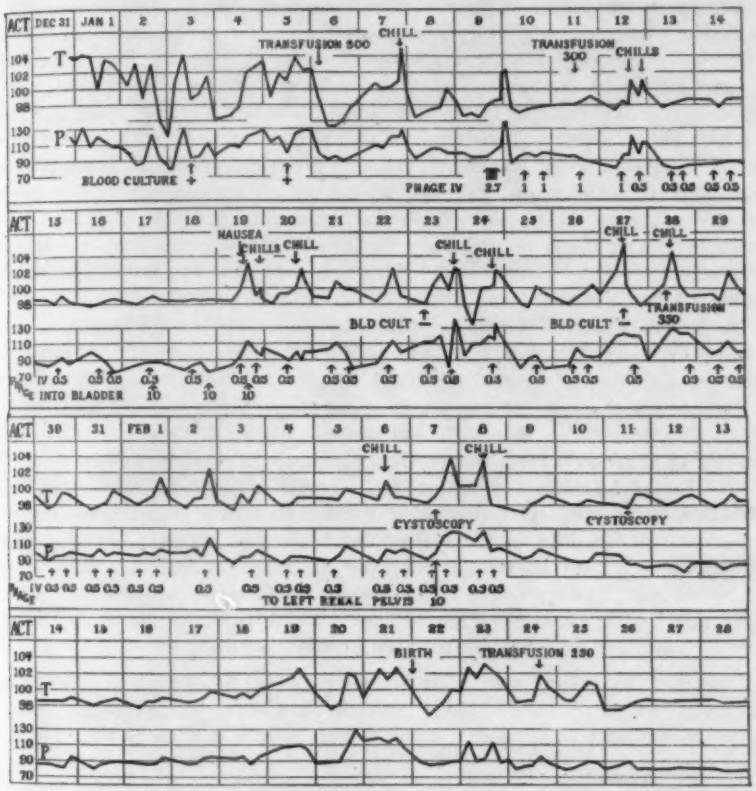

Chart 3 (case 4).—Abridged clinical chart for A. C. T.

of 300 cc. of blood was given on January 6; one of 300 cc. on January 11; one of 350 cc. on January 28, and one of 250 cc. on February 24. Bacteriophage treatment was begun on January 9, on which day four intravenous injections of the asparagine preparation were given, the total amount being 2.7 cc. The intravenous administration of bacteriophage was continued in smaller doses every day until February 8. The reaction of the urine was adjusted, beginning on January 16, by oral administration of potassium citrate, controlled by daily determination of the p_H of the urine, which remained between 6.6 and 7.2 after January 19. Ten cubic centimeters of the broth preparation of bacteriophage diluted with saline solution was introduced into the bladder on January 17, 18 and 19, and bacterio-

phage was introduced into the left renal pelvis on February 7. The clinical chart suggests that these local applications were not particularly beneficial to the patient. The blood chemistry revealed no abnormalities at any time. The most extreme leukocytosis was observed on January 28, when there were 30,700 white cells and 80 per cent polymorphonuclears together with 12 per cent metamyelocytes. A blood culture taken on January 23 and another taken on January 27 remained negative. The urine cultures, however, remained persistently positive for colon bacilli on January 10, 13, 16 and 26 and February 1. A roentgenogram on January 24 revealed slight enlargement of the left kidney.

Because of the persistent urinary infection and absence of other serious disease, the patient was transferred to the urologic service in the same hospital on February 7, in good general condition. A pyelogram made on February 7 revealed dilatation and kinking of the left ureter, dilatation of the left renal pelvis and questionable evidence of a calculus in the left kidney; on the right side there was slight dilatation of the ureter and the renal pelvis. Urine from the left ureteral catheter gave a growth of colon bacilli, as did that from the bladder. Urine from the right ureteral catheter was negative on culture. Bacteriophage was introduced into the left renal pelvis on February 7 after the specimens had been taken. Ureteral catheterization on February 11 showed sterile urine coming from both renal pelves, but the bladder urine still contained colon bacilli and an excessive number of leukocytes.

On February 21 the patient went into labor. A boy was delivered at 12:10 a. m. on February 22 and died at 1:22 a. m. After an uneventful puerperium, the patient was discharged from the hospital free from symptoms on March 5.

The patient came to the laboratory at the New York Post-Graduate Medical School and Hospital on March 30, and we obtained a satisfactory uncontaminated specimen of urine from the bladder. This contained moderately numerous pus cells and rod-shaped bacteria, and cultures of it revealed 15,000,000 colonies per cubic centimeter. The organism proved to be a colon bacillus of the communis variety, similar to that obtained in the earlier blood cultures. It was recommended to her physician that an attempt to eradicate the infection from the urinary tract be undertaken. The patient was free from distressing symptoms but appeared rather thin and weak at the time of her visit. Apparently she, as well as her relatives, wished to postpone further treatment for a time.

Case 5.—This patient was in the Morrisania Hospital, service of Dr. Clarence H. Smith. Repeated positive blood cultures were obtained. A radical operation on the mastoid with removal of a septic thrombus from the lateral sinus and from the jugular vein revealed in these situations the same colon bacillus as was found in the blood stream. The colon bacteriophage was given by intramuscular and intravenous injection and by local application to the wound. The patient died about June 14. The autopsy revealed extensive pneumonia and purulent pyelitis. Further details in regard to this case are not yet available.

COMMENT

From this rather limited experience we feel justified in urging the intravenous use of an asparagine preparation of colon bacteriophage in colon bacillus septicemia. In four of these cases the microbe present in the blood stream was found to be susceptible to lysis by our stock colon bacteriophage. In the fifth case (Dr. Smith's) the bacteriologic studies were carried out elsewhere, and we did not have opportunity for ade-

quate study of the infecting microbe. These findings suggest that organisms of this group virulent enough to produce septicemia are in general more likely to prove susceptible to bacteriophage than those found in the intestine or in the urinary tract. Whether there is an actual correlation between the virulence of the microbe and its susceptibility to bacteriophage cannot be decided from this evidence alone, but the suggestion appears to be of some interest.

It seems wise to begin treatment with a stock bacteriophage as soon as the specific nature of the organism in the blood culture has been recognized. At the same time, the testing of this culture against the bacteriophage and the preparation of a specific bacteriophage by filtration of lysed cultures of the specific microbic strain should be pushed as rapidly as possible in the laboratory, and as soon as such a specific preparation is ready it should be used in place of the stock bacteriophage.

SUMMARY

Septicemia due to the colon bacillus is a disorder of sufficient gravity to invite effective cooperation in its treatment.

The control of the bacteremia appears somewhat easier in the case of the colon bacillus than in the case of the staphylococcus.

Of the five patients observed, one made a complete recovery; two recovered from the bacteremia and left the hospital with persistent bacilluria, and two died.

Bacteriophages potent against colon bacilli may, according to our limited experience, be of some assistance in the treatment of colon bacillus septicemia.

IV. BACTERIOPHAGES IN CHRONIC COLITIS OF UNDETERMINED CAUSATION AND IN INTESTINAL FISTULAS

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AND

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NEW YORK

In an earlier paper we emphasized the need of specific etiologic diagnosis as a prerequisite for the intelligent use of bacteriophages in the treatment of infections. This point of view requires no defense. It is well, however, to recognize that human disease may not infrequently present a problem which defies satisfactory scientific elucidation and that the physician may be required to assume the responsibility for the treatment of a patient whose disorder is only imperfectly understood.

We feel that some apology is required as an introduction to the discussion of the application of bacteriophages in the treatment of the often obscure, nonspecific types of chronic inflammation of the large intestine and of fistulous tracts through which are passing the multitudes of intermingled micro-organisms and heterogeneous remnants of food in the human feces. In some instances it may be possible to recognize among the microbes an individual species of outstanding importance in the causation of the active infectious process, as for example Shigella dysenteriae, the endameba of dysentery or the tubercle bacillus. Certainly the search for these specific causative agents should not be neglected, and when one or the other is detected this knowledge becomes paramount as a guide in combating the disease. Unfortunately, particularly in the bacillary dysenteries, the original specific microbic agent is detected with difficulty after the first few weeks or even after the first week of the disease. Apparently its numbers are greatly reduced, and it appears reasonable to assume that the continuing inflammatory process is caused in part by secondary invaders, intestinal bacteria ordinarily harmless to the intact intestinal wall, but injurious to the deeper structures after the integrity of the protective epithelial covering has been disturbed. The varieties of colon bacillus and staphylococcus appear

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These studies have been aided by a grant from the Josiah Macy Jr. Foundation.

From the Department of Pathology and Bacteriology, New York Post-Graduate Medical School and Hospital, Columbia University.

readily to take up the rôle of secondary invaders. The human intestinal flora is a mixture of various microbes from the early days of extrauterine life. One may therefore find some justification for the idea that by overcoming a few of these microbic species or even only one of them it may be possible to change conditions at the site of the lesions so that the balance may be tipped in the direction of healing. On ideas such as this one attempts to base an excuse for the empirical use of bacteriophages in nonspecific intestinal inflammations and fecal fistulas and in such argument to find a reason for the occasional success which follows the treatment. But even in the absence of a logical explanation or excuse a favorable factor in the treatment of an afflicted human being makes an emotional appeal which may defy intellectual opposition, a situation which gives long life to quackery and charlatanism. We are conscious that the case records to be presented may expose us to some unfavorable criticism on this score, which does not, however, give us great concern.

CHRONIC COLITIS

We have records of fourteen patients who suffered from stubborn disease of the alimentary system, diagnosed as chronic colitis and treated with preparations of bacteriophage. In seven there was definite clinical improvement. In six the result of treatment has not been reported to us. One patient who is under observation was treated with bacteriophage for several months with little or no evidence of relief. Few of these patients have been under observation in the hospital, and on that account the records lack detail and precision. The available records of four of the more fortunate patients will be briefly presented in order to illustrate the methods of application of the bacteriophages and the course of the disorder.

REPORTS OF CASES

CASE 1.—E. S., a boy, aged 9½ years, a patient of Dr. Saul J. Selkin, was suffering from persistent diarrhea. The hemolytic colon bacillus of the variety communis was found predominant in the stool on Feb. 25, 1932, and after three serial filtrations a bacteriophage became fairly potent against this bacillus. The bacteriophage filtrate was mixed with other bacteriophages active against dysentery, proteus and pyocyaneus bacilli. The mixture was given by mouth three times a day in doses of 2 cc., and as retention colonic irrigation in doses of 10 cc. every forty-eight hours for a period of approximately two weeks. The patient was then much improved and returned to school. Subsequently he became entirely well. Further information in regard to this patient is not available.

CASE 2.—E. H., a white girl, aged 13 years, the daughter of a physician and a patient of Dr. E. F. Henderson of New Castle, Pa., had suffered from intractable ulcerative colitis for eight years. She had been under the care of various specialists. On March 24, 1932, we supplied a mixed bacteriophage to be taken by mouth in doses of 2 cc. On March 30 we received a specimen of the stool, the cultures of which yielded predominant colon bacilli of the lactic acid variety, streptococci

producing a narrow zone of hemolysis on blood agar and enterococci. The physician reported clinical improvement on April 4 and again on April 13. By April 25 the girl had gained 5 pounds (2.3 Kg.), and the number of stools was now two or three a day instead of from ten to fourteen a day. The bacteriophage was discontinued for one week, and the frequency of defecation again increased, the number of stools reaching ten a day. With resumption of the bacteriophage therapy a decrease occurred to two stools a day. The bacteriophage treatment was continued until the last of August, when it was stopped. During this time the girl was in better general health than at any time in eight years. In March, 1933, the physician reported that for the first time in her life the girl had attended school regularly since the previous fall and had gained 17 pounds (7.7 Kg.). She continued to take bismuth daily and was also taking cod liver oil. Dr. Henderson ascribes the improvement chiefly to the use of the bacteriophage. His judgment commands respect because of his intimate knowledge of the case over a period of many years.

CASE 3.—S. K., a white boy, aged 2 years and 5 months, was admitted on Aug. 4, 1931, to the service of Dr. R. H. Dennett. The child was born March 20, 1929, was breast fed for ten months, and developed in a normal manner until July 31, 1931, when he suddenly became ill with vomiting, diarrhea, restlessness and fever between 102 and 105 F. On the day preceding the onset of illness, the child ate six tomatoes, some corn and other foods. Bacteriologic examination of a stool passed on August 6 failed to disclose any dysentery organisms. The most abundant bacteria in the cultures were staphylococci, diphtheroids and colon bacilli of the lactis-aerogenes variety. On August 20 and 24 an examination for amebas, intestinal worms and eggs of worms yielded negative results. Many pus cells were present in the stools. A specimen obtained from the rectum by proctoscopy on August 31 yielded, on culture, predominating streptococci producing green colonies on blood agar. There were also abundant colon bacilli of the lactic acid and lactis-aerogenes varieties. The specific microbic factors in the illness were not disclosed by these laboratory studies.

The course of the temperature and pulse rate and number of stools each day are shown in chart 1. The child did not progress for the first five days. On August 8 a transfusion of 200 cc. of blood was given at 10:25 a. m.; at 3 p. m. on the same day broth of a bacteriophage mixture, 10 cc., mixed with milk, was given by mouth and a small retention enema containing 10 cc. of the bacteriophage mixture was introduced into the colon. The mixture was of the shotgun variety, composed of antidysentery bacteriophage, 2 parts, anticoli bacteriophage, 6 parts, and antiproteus, antistaphylococcus, antistreptococcus and antipyocyaneus bacteriophage, each 1 part. The material given by mouth was retained, but the enema was almost immediately expelled although the patient was in a bed set in the position for shock. In fact, the enema evidently irritated the sensitive mucous membrane of the rectum, which was already slightly prolapsed, so that the number of stools on this day rose to sixteen. However, improvement in the clinical condition of the patient and in the temperature and pulse rate seemed to begin immediately. On August 9 the bacteriophage mixture was again given by mouth in the milk: 10 cc. at 10 a. m. and again at 3 p. m. A retention enema containing 10 cc. of the bacteriophage mixture was again quickly expelled. Subsequently the bacteriophage was given only by mouth. The stools, previously watery and green or brown, showed some improvement, being at times yellow and occasionally semiformed, with visible mucus. However, the diarrhea continued, although the general condition of the child improved. Bacteriophage therapy was discontinued on August 26, and on August 27 the feeding formula was limited to evaporated

milk exclusively, which was supplemented with zwieback on September 5 and farina on September 7. After September 1 the diarrhea disappeared, and the patient was discharged in good condition on September 22. He returned to the outpatient department once a month until May, 1933, and during this interval had remained in good condition, with only occasional colds in the head.

CASE 4.—H. G., a white woman, aged 47, unmarried, was admitted to the Long Island College Hospital on Dec. 19, 1930, to the service of Dr. L. F. Warren.[1] Diarrhea and weakness had become progressively worse during the preceding three weeks. The weight on admission was 113 pounds (51.3 Kg.), which had been the normal weight. Examination of the stools for Endamoeba and for dysentery bacilli gave negative results; an abundance of pyocyaneus bacilli was found. Camphorated tincture of opium and acetyltannic acid and later acidophilus milk were given by mouth. Rectal irrigations of silver nitrate, 1:3,000, and plain water were also

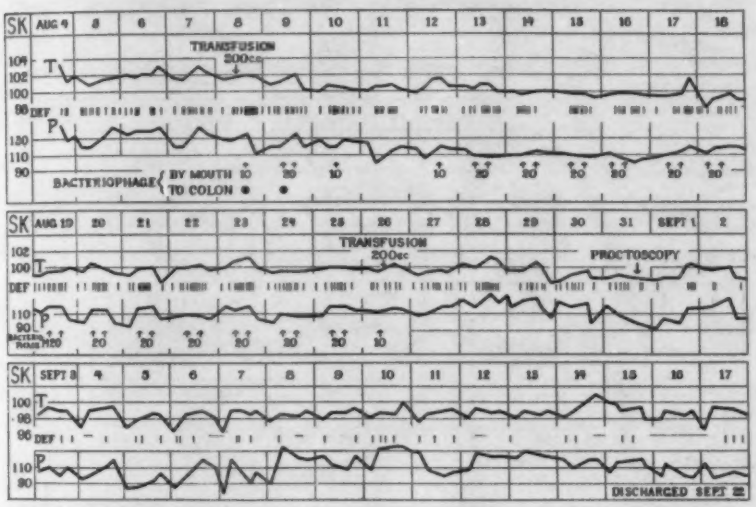


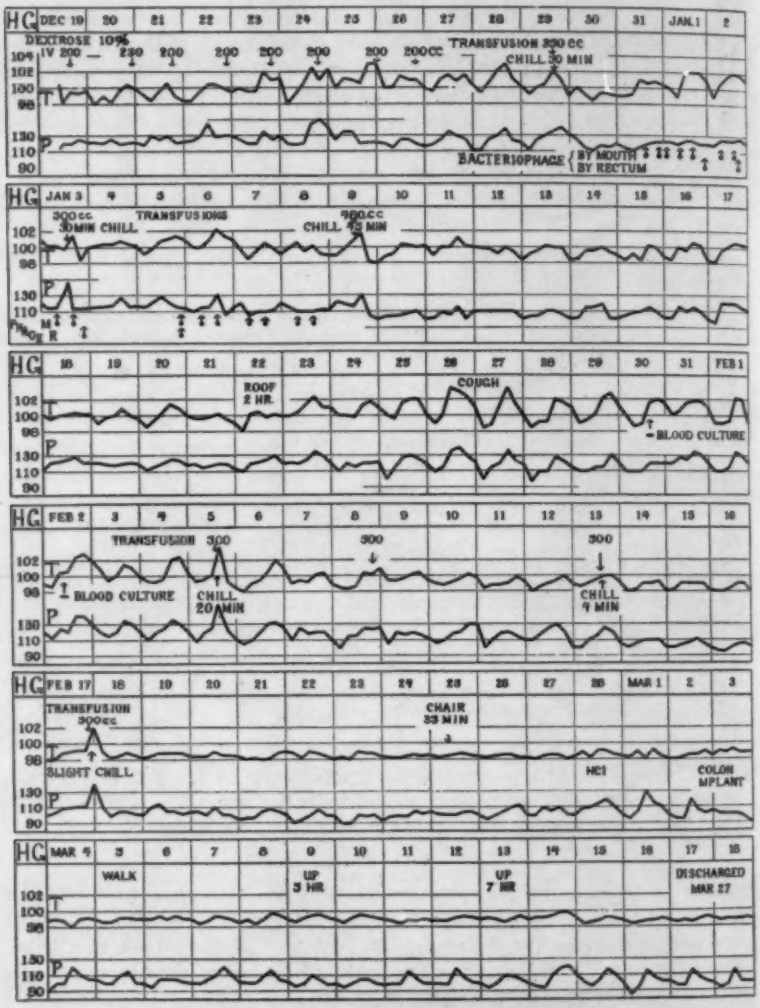
Chart 1 (case 3).—The course of the temperature (*T*), pulse rate (*P*) and number of stools (*DEF*) each day, and the amount and time of administration of bacteriophage and transfusions of blood.

administered. Uncontrolled diarrhea continued with from four to thirty liquid stools a day, and the patient continued to lose strength and weight. Sores from pressure were present on the buttocks. On December 27 the patient was delirious and defecation was involuntary. On December 28 abdominal distention and edema of the lower extremities were noted. A transfusion of blood given at 4 p. m., on December 29 was followed at 4:45 p. m. by a chill which continued to 5:35 p. m. On December 30 the patient was moribund. She was delirious and passed five involuntary stools during the following night. On the morning of December 31 the pulse rate was stronger.

A mixed bacteriophage potent against colon bacilli, dysentery bacilli, staphylococci and some varieties of streptococci was made up on December 30 and was given to the patient by mouth on December 31 at 3 p. m. and again at 10 p. m.

1. Dr. Warren provided the record of the course of this patient.

Subsequently it was given once, twice or three times a day, with the exception of the period from January 4 until January 6. The same mixture of bacteriophage was introduced into the rectum on January 1, 2, 3 and 5, but it was expelled very soon in each instance. The rectal mucous membrane appeared to be very sensitive.


HC
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TRANSFUSION 300
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BLOOD CULTURE
CHILL 20 MIN
CHILL 9 MIN
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SLIGHT CHILL
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COLON IMPLANT
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WALK
UP 5 HR
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DISCHARGED MAR 27
T
P

Chart 2 (case 4).—The course, including temperature and pulse rate, and the administration of bacteriophage.

On January 7 bacteriophage potent against proteus bacilli was added to the mixture and was given by mouth twice on January 7 and twice on January 8. Definite clinical improvement took place during this time. The stools, which had been watery, now became mushy or even partly formed. A clinical note dated January 9 said that the patient looked better. Up to this time she had received sixteen treatments with the original mixed bacteriophage and nine treatments with that con-

taining the proteus bacteriophage.[2] Clinical notes on January 13, 14 and 15 and subsequent days record continued improvement in the general clinical condition and in the character of the stools. The amount of food was increased. Transfusions on December 29 and January 3 and 9 were followed in each instance by a chill. Chills also followed the later transfusions on February 5, 13 and 17.

Apparently there was a complicating infection of the upper respiratory tract about January 26.

Gain in strength was very slow. The frequency of defecation continued, but the stools became less liquid and of smaller volume. A culture of colon bacilli was introduced into the rectum on March 2 and March 3. The patient was discharged from the hospital on March 27, 1931. In a letter dated June 6, 1931, the patient reported that she felt well and had a good appetite, but still had trouble with her bowels, "expelling gas and squirts during the day as many as eight times, but at night maybe once or twice."

PATIENTS WITH INTESTINAL FISTULA

In conjunction with these cases of chronic colitis it seems proper to present the summarized records of two patients, in each of whom a fecal fistula developed following difficult surgical treatment of a complicated disease of the pelvis. In each of these the use of bacteriophages seems to have been one factor in changing an apparently progressive downward postoperative course into a rather discouraging state characterized by lack of progress in either direction, which was finally transformed into slow improvement and eventual restoration to health. The complete hospital records of these patients are available, and exemplify the behavior of patients suffering from mixed infection with intestinal bacteria when treated with bacteriophage.

Case 5.—J. F., a white woman, aged 44, was admitted on July 19, 1931, to the service of Dr. John F. Erdmann. In 1916, after a repair of the perineum and suspension of the uterus, the patient had been informed that she had a tumor in the pelvis situated between the rectum and the spinal column. This caused no discomfort and was neglected until May, 1930, when, following a cold, there was retention of urine requiring catheterization. From July to October, 1930, the patient received some roentgen treatment. On July 21, 1931, a laparotomy was performed which lasted ninety minutes. Included in the operation were subtotal hysterectomy, bilateral salpingo-oophorectomy, removal of a partly disintegrated tumor posterior to the rectum and involving the left ureter, implantation of the left ureter into the bladder at a new site and incision between the coccyx and the anus for the removal of part of the disintegrating tumor mass and for drainage of the pelvic cavity. There were multiple fibroids of the uterus. The disintegrating tumor in the back of the pelvis was regarded at the time of the operation as a malignant process. Subsequent study in the laboratory failed to disclose evidence of malignancy. The growth appeared to be a partly necrotic cystic mass of unusual character.

The postoperative course was stormy. There was blood in the urine on July 22, and frequent vomiting occurred. On July 30 there was a foul odor from the

2. This note was made by Dr. Warren. It does not check exactly with the record on the chart, but the latter may be erroneous.

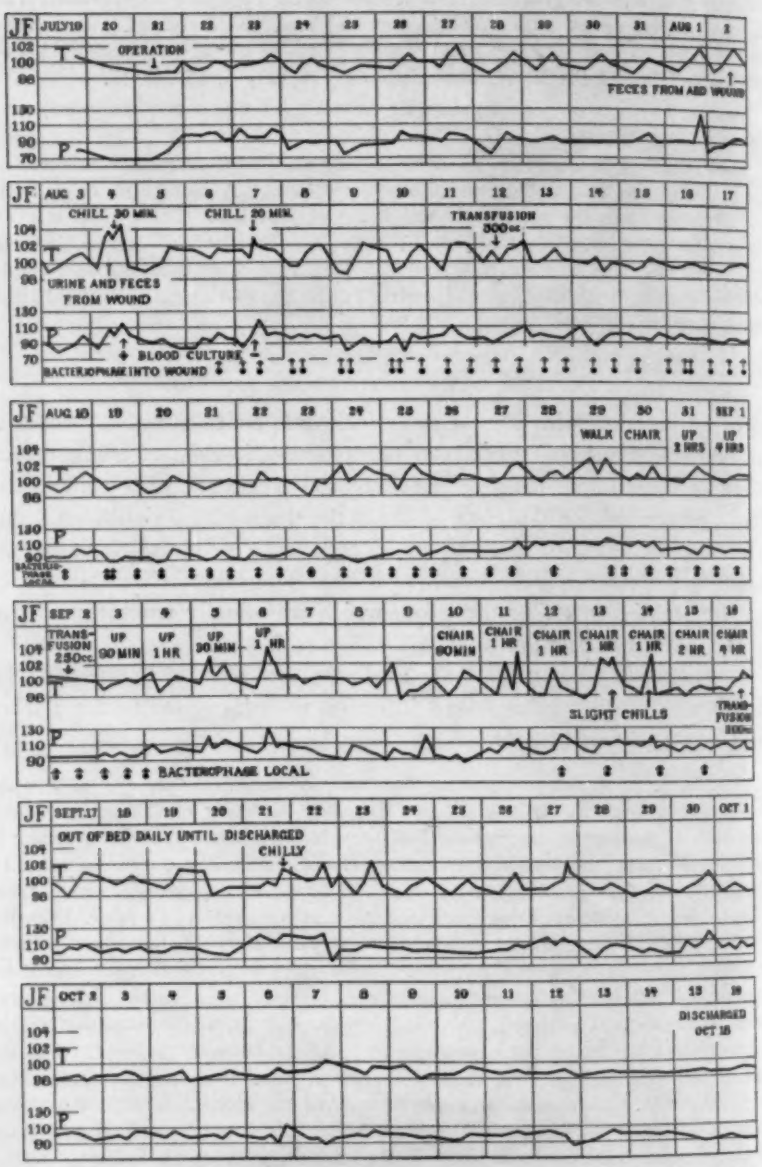
JF
JULY 19 20 21 22 23 24 25 26 27 28 29 30 31 AUG 1 2
OPERATION
FECES FROM ABD WOUND
AUG 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17
CHILL 30 MIN.
CHILL 20 MIN.
TRANSFUSION 300cc
URINE AND FECES FROM WOUND
BLOOD CULTURE
BACTERIOPHAGE INTO WOUND
AUG 19 20 21 22 23 24 25 26 27 28 29 30 31 SEP 1
WALK
CHAIR
UP 2 HRS
UP 4 HRS
SEP 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
TRANSFUSION 250cc
UP 30 MIN
UP 1 HR
UP 30 MIN
UP 1 HR
CHAIR 60MIN
CHAIR 1 HR
CHAIR 1 HR
CHAIR 1 HR
CHAIR 1 HR
CHAIR 2 HR
CHAIR 4 HR
SLIGHT CHILLS
TRANSFUSION
BACTERIOPHAGE LOCAL
SEPT. 17 18 19 20 21 22 23 24 25 26 27 28 29 30 OCT 1
OUT OF BED DAILY UNTIL DISCHARGED
CHILLY
OCT 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
DISCHARGED OCT 15
T
P

Chart 3 (case 5).—The course, including temperature and pulse rate, and the administration of bacteriophage.

abdominal wound, and on August 2 fecal material was recognized on the dressing of the wound. On August 4 both urine and feces were recognized coming from the abdominal wound. On this day there was a chill lasting thirty minutes and a rise of temperature to 104.4 F. A blood culture taken at this time gave a growth of a paracolon bacillus, type undetermined. Cultures from the abdominal wound on August 5 revealed mixed infection. The dominant organisms in the plate cultures were colon bacilli of the lactic acid variety, staphylococci and paracolon bacilli. It was possible to find potent bacteriophages for the colon bacillus and the staphylococcus, but not for the paracolon bacillus.

On August 6 a broth-bacteriophage mixture active against the colon bacillus and the staphylococcus was introduced into the abdominal wound and once, twice or three time a day thereafter until September 4. On August 7 there was a chill lasting for twenty minutes. A blood culture taken at this time remained negative. Transfusions of blood were given: 500 cc. on August 12 and 250 cc. on September 2. Cultures of the urine on August 21 revealed colon bacilli of the lactic acid variety, staphylococci and paracolon bacilli in abundance. The paracolon bacillus was evidently playing an important rôle. Unfortunately we were unable to find a bacteriophage potent against it. Cultures from the wound on September 1 yielded a colon bacillus of the lactic acid variety and Bacillus pyocyaneus. Neither of these was susceptible to bacteriophage races in the laboratory. Another culture from the wound on September 11 yielded Escherichia acidi-lactici, resistant to our bacteriophage races, and an enterococcus in the broth culture. In spite of these unpromising laboratory findings, the mixed bacteriophage was again applied to the abdominal wound daily from September 12 to September 15. On September 16 a transfusion of 500 cc. of blood was given. The patient was now out of bed daily until discharged on October 18.

In this patient the fistulous tract apparently communicated with both the intestines and the bladder. Urine was observed on the abdominal dressing repeatedly from July 31 to September 28, and fecal material from August 2 to September 26. After September 28 neither of these was again recognized on the dressing.

Case 6.—C. H., a white woman, aged 34, a patient of Dr. Eilif C. Hanssen, was admitted on June 29, 1931. Colpotomy was performed on July 1, the incision opening into a large pelvic abscess. Bacteriologic examination of the pus from this abscess revealed Streptococcus viridans and a gram-positive anaerobic bacillus, not further identified. After improvement for two or three days the clinical condition again became unsatisfactory, and on July 6 there was a chill lasting for twenty minutes, with a rise of temperature to 106.2 F. A blood culture taken at this time remained negative. Streptococcus serum, 30 cc., was given on the evening of July 6 and a transfusion of 500 cc. on July 7.

On July 10 the abdomen was opened by incision in the midline, and an infected papillary cyst of the right ovary was aspirated and partly removed. Because of dense adhesions, part of the wall of the cyst was not excised. Drainage was established through the abdominal wall as well as through the vaginal vault. Bacteriologic study of the contents of the cyst revealed colon bacilli of the lactis-aerogenes type and a few hemolytic streptococci. Histologic study of the cyst wall showed it to be an ovarian papillary cystadenoma. Following the operation a transfusion of 500 cc. of blood was given. The postoperative course was fairly satisfactory until July 14, when part of an enema being given by the nurse escaped through the abdominal incision, and on changing the dressings a large amount of fecal material was found in the wound and on the dressing. A blood culture taken on July 15 remained negative. A transfusion of 500 cc. of blood was given on

July 20. Urticaria appearing on July 21 and 22 may have been related to the dose of streptococcus serum given on July 6, although fifteen days had elapsed.

Bacteriophages were employed for the first time on July 25. On this day a specimen of exudate from the abdominal fistula was taken for bacteriologic study, and then, without awaiting the results of this examination, a broth mixture of stock bacteriophages potent against the colon bacillus, staphylococcus and streptococcus and B. pyocyaneus was employed to irrigate the sinus. On July 26 the

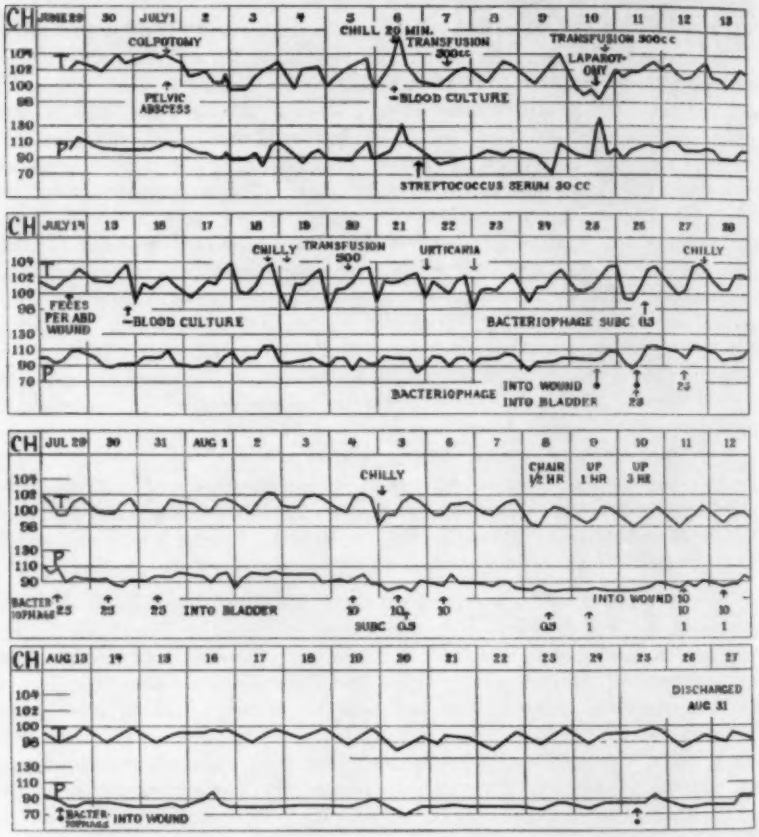

Chart 4 (case 6).—The course, including temperature and pulse rate, and the administration of bacteriophage.

fistulous tract was again irrigated with the same bacteriophage mixture, and 25 cc. of it was introduced into the bladder by a catheter and left there. On July 27 the fistulous tract was irrigated with 25 cc. of the bacteriophage mixture, and the mixture was introduced into the bladder in amounts of 25 cc. on July 29, 30 and 31. A subcutaneous dose of 0.5 cc. of the broth-bacteriophage preparation was given on July 26. There was a slight febrile reaction, apparently related to the subcutaneous injection. By July 29 there was distinct evidence of improvement in temperature, pulse rate and clinical condition.

The specimen of exudate from the fistula obtained on July 25 gave abundant growth of colon bacilli, among which the lactic acid variety was predominant. A specimen of urine obtained from the bladder on July 26, previous to the intravesical bacteriophage treatment, contained many pus cells, and the cultures yielded colon bacilli of the communis variety. A potent specific bacteriophage against this organism was prepared by serial filtration.

The administration of potassium citrate by mouth had been started on July 25, and the dose of this agent was adjusted so as to keep the urine nearly neutral in reaction. Red and blue litmus paper, phenolsulphonphthalein and bromcresol purple, with suitable comparators, were employed to test the reaction of the urine.

On August 4 the use of the newly prepared bacteriophage specific for the colon bacillus in the bladder was initiated. Five instillations of 10 cc. of the preparation were given into the bladder on August 4, 5, 6, 11 and 12, respectively. Five subcutaneous injections of the same preparation were also given: a dose of 0.5 cc. on August 5 and again on August 8 and doses of 1 cc. each on August 9, 11 and 12. The bacteriophage preparation of mixed stock was employed to irrigate the fistulous tract on August 11 and 13 and again on August 25.

Bacterial counts on urine from the bladder showed 276,000,000 per cubic centimeter on August 5, 7,400,000 on August 6, 162,000,000 on August 11, 72,000,000 on August 12 and 327,500,000 on August 24. The predominating organism in the last specimen was a colon bacillus of the lactic acid variety which was only partially susceptible to the bacteriophage used.

The clinical course was that of gradual improvement. Fecal material was recognized on the dressings of the abdominal wound on August 4 for the last time. After August 12 the temperature was always below 100 F. until the patient was discharged on August 31. The sinus in the abdominal wall was still secreting a small amount of exudate on August 31. On Oct. 21, 1931, she was seen by Dr. Hanssen. She had gained 20 pounds (9.1 Kg.) and the sinus was almost healed. On May 11, 1933, in response to a follow-up inquiry, she reported herself as well and steadily at work. The physician in attendance and those who saw this patient in consultation have expressed conviction that the bacteriophage therapy was of distinct service in this case.

COMMENT

In the introductory paragraphs we expressed some diffidence about presenting the records of these patients, because it seemed to us that a claim of a favorable effect of treatment by bacteriophage in these cases rests on evidence distinctly less convincing when compared with the observations on septicemia and on infections of the urinary tract. The problem of mixed infections presents complex difficulties to the bacteriologist who has been trained to a wholesome skepticism based on the postulates of Henle and of Koch.

The apparent favorable influence of the preparations of bacteriophage in these patients may have resulted: (1) from an actual destructive and restraining influence on the infecting microbe; (2) from a psychic encouragement of the patient who may be emotionally influenced by the thought of a mysterious agent which is capable of seeking out and opposing his microbic enemies, or (3) from a stimulus to more precise and more enthusiastic general clinical care by the physician because a

problematic and interesting new therapeutic agent had been made available. We are inclined to think that all three of these factors may play a part in the ultimate outcome of a case. Especially important is the enthusiasm of the clinician who is actually at the bedside. If he is not interested and does not welcome the aid of the bacteriophages it is easily possible to fail in the treatment.

As far as we have observed, the use of preparations of bacteriophage by mouth or by injection into fistulous tracts is without untoward effects. On the other hand, there is some evidence to indicate an irritant effect when these are introduced through a colonic tube into the inflamed intestine, and there is convincing proof that local irritation and a general rise in temperature may follow subcutaneous or intramuscular injection. In the group of cases reported in this paper serious untoward effects which could be ascribed to the use of the bacteriophages were not observed.

SUMMARY

The empirical use of preparations of bacteriophage potent against some of the intestinal microbes has been followed by favorable results in patients suffering from chronic colitis of undetermined causation. Because of the evident harmless nature of this therapy, it would appear worthy of trial in this sometimes baffling condition. Postoperative intestinal fistulas infected with a mixture of intestinal bacteria have been, in two instances, favorably influenced by the use of bacteriophages active against the intestinal bacteria.

The therapeutic results are not dramatic. The bacteriophages seem rather to exercise a merely beneficent influence on the course of the essentially chronic ailment.

EFFECT OF EPINEPHRINE ON THE SYMPATHECTOMIZED HUMAN EXTREMITY

AN ADDITIONAL CAUSE OF FAILURE OF OPERATIONS FOR RAYNAUD'S DISEASE

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AND

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We have recently observed a recurrence of vascular spasm after complete sympathectomy in a number of cases of Raynaud's disease; in two instances the recurrence appeared within two weeks after the operation. In 1905 Elliott [1] showed that in animals structures innervated by the sympathetic nervous system become sensitized to epinephrine after denervation, and the theory was recently emphasized by Rosenblueth and Cannon.[2] We have carried out a series of experiments on human beings and on animals, the results of which are given in this communication and which we believe show that recurrence of vascular spasm after complete sympathectomy, in man as well as in animals, is probably due to sensitization of the sympathectomized extremities to epinephrine.

Sympathetic ganglionectomy for vascular disease of the extremities has been performed in seventy-five cases by the members of the clinic for circulatory diseases of the Massachusetts General Hospital. The great majority of these operations have been performed for vascular spasm, although we have operated on a few patients with underlying obliterative vascular disease in whom the element of vascular spasm was striking.

The immediate results have been very satisfactory,[3] but the same cannot be said of the end-results.[4] We have found the beneficial effect

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From the surgical services of the Massachusetts General Hospital.

Dr. Bradford Cannon and Dr. Henry Heyl assisted in carrying out the tests in a number of the cases studied.

1. Elliott, T. R.: The Action of Adrenalin, J. Physiol. **32**:401, 1905.

2. Rosenblueth, A., and Cannon, W. B.: Studies on Conditions of Activity in Endocrine Glands; Some Effects of Sympathin on the Nictitating Membrane, Am. J. Physiol **99**:398 (Jan.) 1932.

3. (*a*) White, J. C.: Experiences with Sympathetic Ganglionectomy in Peripheral Circulatory Disease, New England J. Med. **204**:852 (April 23) 1931; (*b*) Raynaud's Disease: Studies on Post-Operative Cases Bearing on the Efficiency of Sympathetic Ganglionectomy, ibid. **206**:1198 (June 9) 1932.

4. Allen, A. W.: Results Obtained in the Treatment of Raynaud's Disease by Sympathetic Neurectomy and in Thromboangiitis Obliterans by Desensitization of Peripheral Sensory Nerves, Ann. Surg. **96**:867 (Nov.) 1932.

of lumbar ganglionectomy to be more permanent than that of dorsal ganglionectomy. To eliminate vascular spasm in the vessels of the lower extremity, we have attempted to remove the lumbar trunk from above the second to below the fourth lumbar ganglion. In the majority of instances, we have removed a portion of the chain which included three ganglions, probably the second, third and fourth lumbar.

At first we believed in common with others that to sympathectomize the upper extremity it was sufficient to remove the first and second or even the second and third dorsal ganglions. The immediate results seemed equally satisfactory, but in the course of from six months to a year, a recurrence of varying degrees of vascular spasm was frequently observed. We believed that this was either because efferent vasoconstrictor impulses were reaching the vessels through pathways which had not been interrupted, or because regeneration of nerve fibers occurred. In a number of these cases further surgical intervention has been resorted to when it was possible to demonstrate by paravertebral procaine hydrochloride block or by other methods that there remained a definite connection between the cervicodorsal sympathetic ganglions and the cords of the brachial plexus. After this connection had been interrupted, there followed a striking rise in peripheral surface temperature and other evidence of a complete sympathectomy in the extremity. As a result of these secondary operations, we have arrived at the belief that in order to sympathectomize the upper extremity it is necessary to remove the sympathetic chain from above the inferior cervical ganglion to below the second dorsal ganglion. This technic has been followed in all our cases during the past year and has recently been reported in another communication.[5]

Following this more complete operation, we have repeatedly noticed the reappearance of vascular spasm at varying intervals. In some patients spasm could be produced by exposure to cold, in response to pain and following emotional stimuli. Another patient was symptom-free for nine months after sympathectomy of both upper extremities, and then vascular spasm developed which resulted in mild gangrene of the tips of two fingers of each hand during the tenth month (fig. 1). This patient's history revealed that during that month she had been caring for a sick relative and had been much upset emotionally. Furthermore, the original appearance of vascular spasm dated from the sudden death of her husband nearly five years previously.

These patients, as well as others, have been put through exhaustive tests [3b] which, we believe, have demonstrated that there has been a com-

5. White, J. C.; Smithwick, R. H.; Mixter, W. J., and Allen, A. W.: A New Muscle Splitting Incision for Resection of the Upper Thoracic Sympathetic Ganglia, Surg., Gynec. & Obst. **56**:651 (March) 1933.

plete interruption of the efferent sympathetic pathways to the extremities in question; this tends to prove that the recurrence of vascular spasm cannot be explained on the basis of either an incomplete surgical procedure or regeneration of nerves. Progress of local disease might be offered as an explanation, but obviously the time element makes this solution highly improbable. The close association of the recurrent spasm with emotional stimuli followed by periods of almost total absence of spasm strongly suggested the direct action on the blood vessels of the circulating hormone, epinephrine. That some patients are able to secrete sufficient epinephrine into the blood stream to produce vasospasm in the sympathectomized area is, we believe, shown by the following experiments.

Fig. 1 (case 2, B. R.).—Gangrene of tips of two fingers of each hand ten months after ganglionectomy. Gangrene appeared during the tenth month while the patient was under prolonged emotional strain. Previous to this the patient had been symptom-free. In this instance the gangrene is presumably caused by vascular spasm in the sensitized areas due to increased secretion of epinephrine in response to emotion.

Nine patients (listed in the table) from our total series have been studied to determine whether their sympathectomized extremities are sensitized to epinephrine. In each instance it has first been shown by procaine hydrochloride block and by other tests whether or not the extremities in question have been completely sympathectomized. The response to epinephrine (figs. 2 and 3) has then been determined by the prolonged intravenous administration of a solution of epinephrine chloride in physiologic solution of sodium chloride in a 1:250,000 dilution, at the rate of from 40 to 60 drops a minute, after first establishing the response to physiologic solution of sodium chloride given intravenously at the same rate and under the same conditions.

Case	Sex	Age	Diagnosis	Operation	Time Since Operation	Degree of Vascular Spasm Following: Epinephrine 1:250,000	Insulin	Clinical Recurrent Spasm
1. L. M.	F	39	Vasomotor spasm with early peripheral arteriosclerosis	Bilateral cervicodorsal ganglionectomy	22 days	Marked	Marked	Marked
				Bilateral lumbar ganglionectomy		Marked	Marked	Slight
2. B. R.	F	44	Raynaud's disease with scleroderma	Bilateral cervicodorsal ganglionectomy	10 months	Marked	Marked	Marked
3. F. McV.	M	32	Raynaud's disease	Right cervicodorsal ganglionectomy	10 days	Marked	Not done	Marked
4. P. B.	F	27	Raynaud's disease	Right dorsal (first and second) ganglionectomy; incomplete operation	3 years	None	None	Marked
5. P. R.	F	20	Vasomotor instability	Bilateral lumbar ganglionectomy	5 months	Moderate	Moderate	None
6. R. F.	F	19	Idiopathic epilepsy	Bilateral cervicodorsal ganglionectomy	12 days	Not done	Marked	.....
7. S. T.	M	41	Bronchial asthma	Left cervicodorsal ganglionectomy	15 months	Moderate	Moderate	.....
8. M. McG.	F	21	Raynaud's disease	Right cervicodorsal ganglionectomy	3 months	Marked	Not done	None
9. R. U.	M	44	Bronchial asthma	Paravertebral injection of alcohol (first, second and third dorsal); marked Horner's syndrome	2 days 6 days 8 days 18 days	None None Mild Moderate	Not done	.....

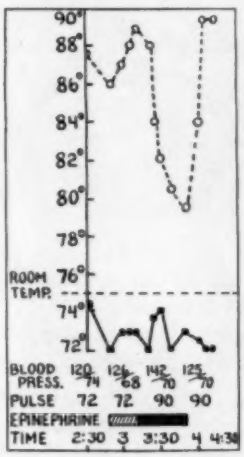

Figure 2

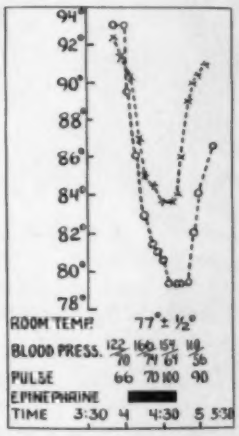

Figure 3

Fig. 2 (case 8, A. McG.).—Raynaud's disease. Typical response to intravenous injection of epinephrine three and one-half months after cervicodorsal ganglionectomy. This chart shows the degree of vascular spasm in the sympathectomized extremity as contrasted with the absence of vascular spasm in the normally innervated extremity. The circles and dotted line indicate the temperature for the denervated third finger of the right hand; the blocks and solid line, the temperature of the normally innervated third toe of the right foot.

Fig. 3 (case 1, L. M.).—Raynaud's disease. The test performed ten weeks after cervicodorsal and three weeks after lumbar ganglionectomy shows a typical response to intravenous administration of epinephrine. Note the degree of vascular spasm in both upper and lower extremities. The circles and dotted line indicate the temperature in the denervated third finger; the crosses and dotted line, the temperature in the denervated third toe.

In view of the fact that hypoglycemia has been shown to stimulate the secretion of epinephrine in animals,[6] it seemed fair to expect a similar reaction in human beings. The concentration of epinephrine in the circulating blood would presumably be temporarily increased and should therefore be accompanied by vascular spasm in the sympathectomized area. This should result in a fall in surface temperature, which was found to occur in every instance. A typical reaction of a sympathectomized extremity during hypoglycemia is represented in figure 4.

The acutely sympathectomized extremity (procaine hydrochloride block) reacts as does a normally innervated extremity (fig. 5); hence

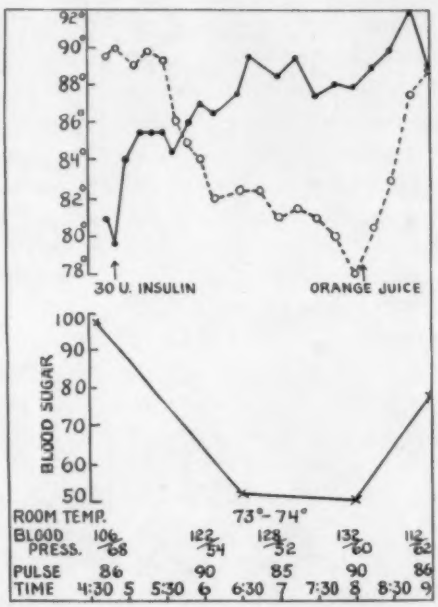

Fig. 4 (case 6, R. F.).—Typical reaction to secretion of epinephrine in insulin hypoglycemia twelve days after a left cervicodorsal ganglionectomy. Note the vascular spasm in the sympathectomized extremity and the absence of spasm in the normal extremity; in fact, the temperature of the normal extremity rose during the experiment. The spasm in the sympathectomized extremity is similar to that shown in figures 2 and 3, but the fall in temperature is more gradual, perhaps because the rise in the amount of epinephrine in the blood is presumably more gradual in response to hypoglycemia than when the substance is injected directly into the blood stream. The open circles and dotted line indicate the temperature in the denervated third finger of the left hand; the solid circles and solid line, the temperature in the normal third finger of the right hand.

6. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: A Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, Am. J. Physiol. **69:** 46 (June) 1924.

it is impossible to predict which patients will have a clinical recurrence of vascular spasm after operation. Figure 5 also illustrates the fact that the incompletely sympathectomized extremity is not sensitized to epinephrine. In this instance (table, case 4) a dorsal ganglionectomy had been performed three years previously in an attempt to sympathectomize an upper extremity for Raynaud's disease. At that time the first and second dorsal ganglions, the intervening trunk and all communicating rami over this extent had been removed. There followed a clinical recurrence of vascular spasm about one year after operation. We believe that this test enables us to prove whether or not an extremity is completely sympathectomized.

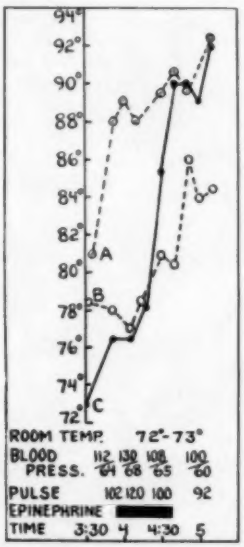

Fig. 5 (case 4, P. B.).—Raynaud's disease. *A*, temperature of the third finger following incomplete sympathectomy of the right arm with reestablishment of vasomotor tone. *B*, temperature following acute denervation of the little finger of the left hand following injection of procaine hydrochloride into the ulnar nerve. *C*, temperature of the normal third finger of the left hand. The right hand, with reestablishment of its sympathetic connections, shows no sensitivity to epinephrine. The acutely denervated finger, in which the sympathetic nerves are paralyzed but have not degenerated, shows complete vasodilatation, but no evidence of sensitization to epinephrine.

At the present time, a series of experiments with animals is in progress to support our clinical data. The results so far are entirely in agreement with those noted in man. It has also been shown in cats and in rabbits that when the right suprarenal gland has been denervated and the left resected, vasospasm in the sympathectomized extremity or

denervated ear which had previously been present during insulin hypoglycemia, was entirely eliminated. These data will be reported in full in another communication.[7]

COMMENT

During the intravenous administration of epinephrine chloride (figs. 2 and 3) in high dilution, 1:250,000, there is a rapid fall in the surface temperature of the sympathectomized extremity. At the same time, the color of the extremity becomes definitely cyanotic, particularly in cases in which some organic obstruction is present in the peripheral vessels. When the administration of epinephrine ceases there is a marked rise in surface temperature of the extremity, and the color becomes normal. The normally innervated extremity shows comparatively little change in surface temperature or color. Following procaine hydrochloride block the acutely sympathectomized extremity does not appear to be sensitized and reacts essentially as does the normally innervated extremity (figs. 2 and 5). The incompletely sympathectomized extremity (fig. 5) also reacts as does a normally innervated extremity.

Insulin hypoglycemia (fig. 4) produces a fall in the surface temperature of the sympathectomized extremity which is similar to that which has been shown to occur with the injection of epinephrine. We have interpreted this as further evidence to support the theory of Cannon, McIver and Bliss [6] that there is hypersecretion of epinephrine into the blood stream in this state. As far as the problem at hand is concerned, we believe that the reaction of the sympathectomized extremity to epinephrine administered intravenously and to insulin hypoglycemia is similar. This suggests that the vascular spasm which accompanies hypoglycemia is due to increased secretion of epinephrine into the patient's blood stream.

We believe that the completely sympathectomized extremity becomes sensitized to epinephrine chloride circulating in the blood stream between seven and eight days after operation (fig. 6).

From a clinical point of view, it is impossible as yet to state the full significance of these findings. It is distressing, to say the least, to find a recurrence of vascular spasm within two weeks after an extremity has been completely sympathectomized. We are not aware of the clinical return of vascular spasm as soon as this after what we now term an incomplete operation. In the earlier cases, recurrence of symptoms in from six months to a year was a frequent occurrence. Whether vascular spasm due to the direct action of epinephrine on the blood vessels after sympathectomy will cause as severe symptoms and

7. Freeman, N. E.; Smithwick, R. H., and White, J. C.: Adrenal Secretion in Man, The Reactions of the Blood Vessels of the Human Extremity, Sensitized by Sympathectomy, to Adrenalin and to Adrenal Secretion Resulting from Insulin Hypoglycemia, Am. J. Physiol. **107**:3 (March) 1934.

as marked circulatory insufficiency as the original disease (spasm due to efferent sympathetic impulses) remains to be seen. We know that it can produce gangrene of the tips of two fingers of each hand (fig. 1). Although we believe that all sympathectomized extremities will be sensitized to epinephrine injected intravenously, we do not believe that every patient will show a clinical return of spasm after an apparently complete operation. Two patients (table, cases 5 and 8) are completely sympathectomized, sensitized to epinephrine, but clinically cured. In cases 1, 2 and 3 there is marked clinical spasm, although in case 1 this spasm is much more noticeable in the upper than in the lower extremities.

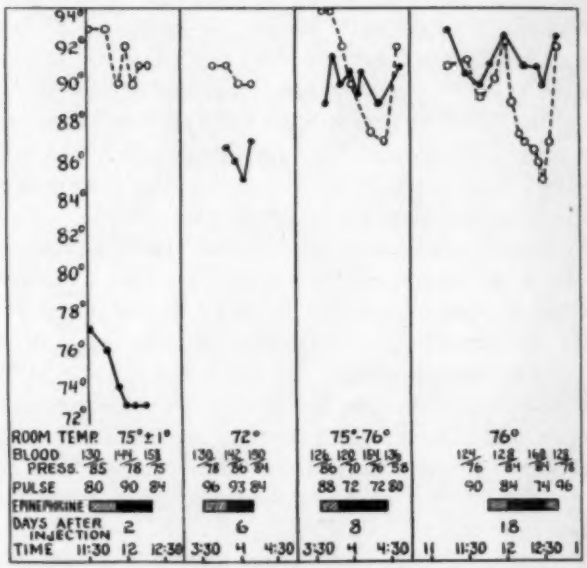

Fig. 6 (case 9, R. U.).—Complete paralysis of the cervicodorsal sympathetic nerves after injection of alcohol for bronchial asthma. These charts illustrate the development of sensitization to circulating epinephrine. Sensitization of the arteries appears between the seventh and eighth days after the injection and is complete by the eighteenth day. The open circles and dotted line indicate the temperature of the denervated fifth finger of the left hand; the solid circles and solid line, the temperature of the normal fifth finger of the right hand.

This spasm appears particularly in response to cold, but also in response to pain and emotional stimuli. The cold threshold seems to be slightly higher than it was before operation, and in general the spasm is less intense and more readily relieved by immersion of the extremities in warm water. This suggests that as far as possible the after-care of these patients should aim toward the production of a state of emotional stability. Freedom from worry and attempts to adjust psychologic problems are undoubtedly important.

From a surgical point of view, complete excision of the medullary portion of the suprarenal glands, sympathectomy of both suprarenal glands or sympathectomy of one and excision of the other may offer a solution. We have performed the latter operation in rabbits and cats in order to prove that the influence of the suprarenal glands on the sympathectomized extremity can be eliminated. Whether this will be followed by some untoward effect on the animals or whether they will be able to lead a comparatively normal life after such an operation can be told only after sufficient time has elapsed. It is possible that the sympathetic nerve supply to the remaining suprarenal gland will regenerate, and it is possible that the liver or some other organ can produce an internal secretion to take the place of epinephrine. In either case the vascular spasm may recur.

SUMMARY AND CONCLUSIONS

1. The fact that in animals structures innervated by the sympathetic nervous system become sensitized to circulating epinephrine following sympathectomy has been shown by Elliott as well as by Rosenblueth and Cannon. Evidence is presented in this report that human blood vessels become sensitized to epinephrine in the same manner following resection of sympathetic ganglions.

2. Tests in a series of nine cases in man following complete sympathetic denervation of extremities have shown marked vasospasm in the presence of minute quantities of epinephrine in the circulating blood. Thus the intravenous infusion of a 1:250,000 solution of epinephrine, an amount which causes little change in the normal extremity, is sufficient to lower the surface temperature of the denervated side as much as 15 F. Similar changes take place when the patient's suprarenal glands are stimulated to secrete epinephrine by insulin hypoglycemia.

3. Identical vasospastic phenomena, which occur in sympathectomized cats and rabbits in insulin hypoglycemia, are abolished by suprarenal denervation.

4. This hypersensitization of the arteries to epinephrine takes place only on degeneration of the vasomotor nerves. It is not present after procaine hydrochloride block or during the first week after operation. We have found that it takes from seven to eight days for sensitization to appear.

5. We believe that this hypersensitivity to the circulating hormone, epinephrine, which develops in sympathectomized extremities, constitutes a hitherto unrecognized but important source of unsatisfactory results in Raynaud's disease.

STRUMA LYMPHOMATOSA (HASHIMOTO) ASSOCIATED WITH HYPERTHYROIDISM

REPORT OF A CASE WITH CLINICAL AND HISTOPATHOLOGIC STUDY

DAVID POLOWE, M.D.
PATERSON, N. J.

The case of struma lymphomatosa which is the subject of this report derives its importance from the fact that it was associated with hyperthyroidism in a young woman. The few cases thus far reported have in common the facts that the pathologic entity was found in women over 40, and that it was associated with no thyroid symptoms other than those that might be ascribed to moderate compression of the trachea. Some authors have observed hypothyroidism and myxedema as late effects. A few authors have felt that one could not exclude hyperthyroidism as an insidious precursor to the disease. As far as I can discover, this is the first case to be reported of struma lymphomatosa associated with hyperthyroidism. As such it furnishes an interesting link, perhaps the first stage in the pathogenesis of the obscure thyroid disease known as the struma lymphomatosa of Hashimoto[1] or the lymphadenoid goiter of Williamson, Scott and Pearse.[2] Thus, evidence is now at hand to show that clinically the reconstructed sequence of events may be: first, a phase of hyperthyroidism; second, a phase of apparently normal thyroid activity which may or may not be associated with symptoms referable to compression of the trachea, and, third, a hypothyroid or myxedematous phase which, also, may or may not be associated with symptoms referable to compression of the trachea. Because of its usually insidious course it is conceivable that struma lymphomatosa may go unnoticed in any of its phases during the life of the patient. The rarity of the condition and the distinctive pathologic process found are sufficient apology for basing this report on one case.

REVIEW OF THE LITERATURE

Struma lymphomatosa was first described by Hashimoto,[1] in 1912. He reported four cases. Williamson, Scott and Pearse,[3] in 1925, while examining two thousand specimens of thyroid tissue for the purpose of classifying them on a pathologic basis, found some glands (the exact

1. Hashimoto, H.: Zur Kenntnis der lymphomatosen Veränderung der Schilddrüse (Struma Lymphomatosa), Arch. f. klin. Chir. **97**:219, 1912.

2. Williamson, G.; Scott, G., and Pearse, I. H.: Lymphadenoid Goitre and Its Clinical Significance, Brit. M. J. **1**:4, 1929.

3. Williamson, G.; Scott, G., and Pearse, I. H.: The Pathological Classification of Goitre, J. Path. & Bact. **28**:361, 1925.

number was not stated) with the distinctive pathologic changes which they termed lymphadenoid goiter. They described the pathologic change in much greater detail in 1929.[2] Ewing,[4] in 1928, stated that he saw four cases of the Hashimoto type, but believed them to be early stages of Riedel's struma, which Riedel reported in 1896. But in his report Riedel made no mention of the extensive infiltration of the gland with lymphocytes and lymph follicles. Joll,[5] in his short chapter on lymphadenoid goiter, gave plausible reasons for considering Riedel's struma an entirely different disease entity from struma lymphomatosa. Graham and McCullagh,[6] in 1931, reported four cases of the Hashimoto type.

ETIOLOGY

The etiology of struma lymphomatosa is obscure. McCarrison,[7] in 1929, produced a condition simulating lymphadenoid goiter. He used rats, and fed them American white flour, meat residue, olive oil and table salt containing a little potassium iodide. It required a few months on this diet to produce the condition. He concluded that deficiency of iodine is not a factor in the production of lymphadenoid goiter, and that deficiency of vitamins is a factor.

PATHOGENESIS

In considering the pathogenesis of struma lymphomatosa it is well to bear in mind the two functions of the thyroid gland: (*a*) the lymphogenic process, the secretion of which does not contain thyroxine and (*b*) the colloid-producing function, in which the colloid contains thyroxine. In struma lymphomatosa, undue strain falls on the lymphogenic process. The replacement fibrosis which occurs, though constant in the later stages, is never the most conspicuous feature of the histologic change. Williamson and his associates describe it with great accuracy as follows:

> The lymphocytic infiltration is peculiar in that it picks out specific thyroid lymph spaces in a most delicately selective fashion. As the disease progresses the lymphogenesis becomes more and more active; lymphocytes begin to collect at the hilum of the gland unit and to arrange themselves in a circular fashion around its circumference as they crowd in the perivascular lymph spaces about the capsule

4. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, p. 961.

5. Joll, Cecil A.: Diseases of the Thyroid Gland, St. Louis, C. V. Mosby Company, 1932, p. 112.

6. Graham, A., and McCullagh, E. P.: Atrophy and Fibrosis Associated with Lymphoid Tissue in the Thyroid: Struma Lymphomatosis (Hashimoto), Arch. Surg. **22**:548 (April) 1931.

7. McCarrison, R.: Note on the Experimental Production of Lymphadenoid Goitre in Rats, Brit. M. J. **1**:5, 1929.

of the gland units. The parenchyma, which produces the lymphogenic secretion, becomes hyperplastic, and active mitosis appears in the epithelium. As the process advances, abnormal lymphogenic activity claims the whole field, and colloid storage becomes inconsiderable. Exhaustion of the epithelium eventually ensues, and now, no longer able to produce secretion, becomes atrophic.

DIAGNOSIS

Clinical recognition of struma lymphomatosa is impossible in the presence of hyperthyroidism, which I consider the earliest stage of the disease. In the later stages the following criteria may help in making a preoperative diagnosis (Graham and McCullagh [6]): 1. There is uniform bilateral firm or hard enlargement of the thyroid gland without notable deformity of the lobes and without definite nodules. 2. There is close attachment of the thyroid gland to the trachea without adherence to overlying structures. 3. It occurs in women in middle life or over. 4. There are no symptoms other than those that might be ascribed to moderate compression of the trachea. 5. There is no impairment of the general health. 6. There is no involvement of regional lymph nodes or evidence of distant metastases. 7. There are no signs of local inflammation.

Joll [5] stated his objections to classifying struma lymphomatosa as an early stage of Riedel's struma as follows: 1. Struma lymphomatosa is confined almost entirely to women over the age of 45. Riedel's struma may appear at any age, and men are affected nearly as often as women. 2. Struma lymphomatosa tends to the development, sooner or later, of myxedema. Riedel's struma rarely leads to hypothyroidism, even after extensive resection of the thyroid gland. 3. Struma lymphomatosa is a diffuse process at the start, no part of the gland escaping. In Riedel's struma, localization to a lobe or part of a lobe is usual. 4. Widespread formation of delicate connective tissue is characteristics of struma lymphomatosa in the advanced stages. Dense fibrosis, comparable to scar tissue, is found in the earliest stages of Riedel's struma. 5. In struma lymphomatosa there is no involvement of the surrounding structures. In Riedel's struma such involvement is characteristic.

REPORT OF A CASE

Miss H. E., aged 26, white, presented herself for examination on July 14, 1933. Her chief complaint was that her doctor told her that she had high blood pressure. She had gone to him with the chief complaint that for the past eighteen months she perspired so profusely that she had to change her clothing several times a day, that she was constipated and that she had been unable to gain weight. Her father died twenty years before of pneumonia. Her mother, aged 63, whom I also examined, was well, but had mild hypertension, with a blood pressure of 170 systolic and 90 diastolic. The mother had a slight, but noticeable enlargement of the left thyroid lobe. The patient's tonsils were removed at the age of 6. Her history was negative otherwise. Her menstrual history was normal and her previous health excellent.

General examination revealed a weight of 110 pounds (50 Kg.), a pulse rate of 120, a blood pressure of 180 systolic and 110 diastolic, slight enlargement of the right thyroid lobe and normal eyegrounds. The central nervous system was normal. Urinalysis disclosed a trace of albumin.

My clinical impression on the first visit was that I was dealing with idiopathic hypertension, possibly nephrosis (the diabetes albuminuricus of Epstein), so I gave the patient a diet high in protein and instructed her to report to me in two weeks.

On the occasion of the second visit, on July 29, I elicited the history of hyperhidrosis and the inability to gain weight. The persistent high pulse rate of 120 and the persistent hypertension of 176 systolic and 108 diastolic called my attention to the slight enlargement of the right thyroid lobe. My diagnosis at this time

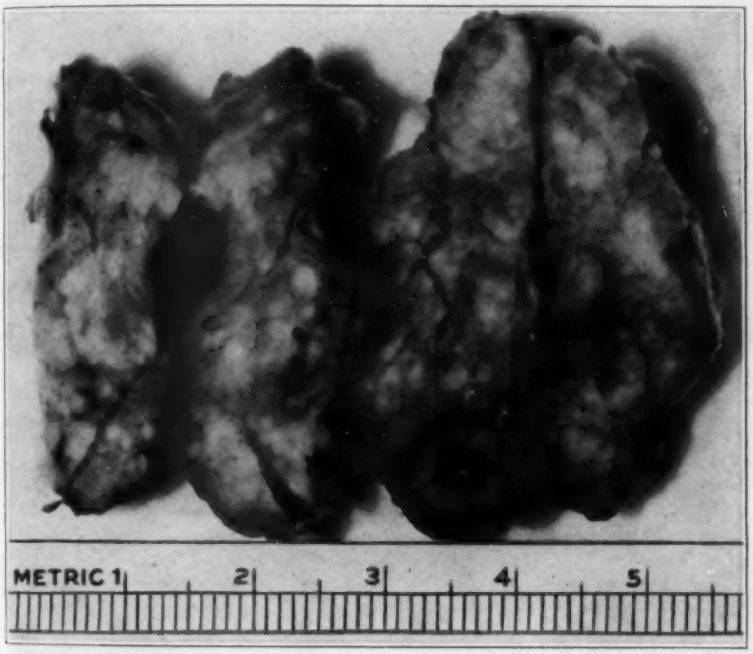

Fig. 1.—Thyroid tissue. The left and right lobes are cut across and opened like a book. The capsule was smooth and nonadherent, and the consistency was firm. The cut surfaces exhibit a gland diffused throughout with small, yellowish-white, opaque lymph follicles, of various sizes. The gland substance is pink between the follicles and poor in colloid; reduced from a magnification of × 2.

was hyperthyroidism with hypertension. Because of the otherwise excellent clinical condition of my patient, her weight being about the same (109.5 pounds [49.8 Kg.]), I permitted her to take a previously planned trip to California. I continued the diet high in protein, advised as much rest as possible and prescribed no thyroid medication. It was understood that on her return tests of thyroid and renal function would be made.

On September 21, the patient reported back to me. A postcard in the interim stated that she felt well. On September 21 she was still feeling well, was not as

constipated as previously and had gained weight. Her weight was 115 pounds (52.3 Kg.), the pulse rate 100, with occasional extrasystoles, and the blood pressure 196 systolic and 112 diastolic.

On September 22, the basal metabolic rate was plus 43, urea nitrogen 15.7 mg. per hundred cubic centimeters of blood, creatinine 1.7 mg. and blood chlorides 515 mg. The urinalysis disclosed a trace of albumin, a few leukocytes, a moderate number of red blood cells and no sugar. I recommended subtotal thyroidectomy, and the patient was hospitalized the following day, at the Barnert Memorial Hospital, Paterson, N. J.

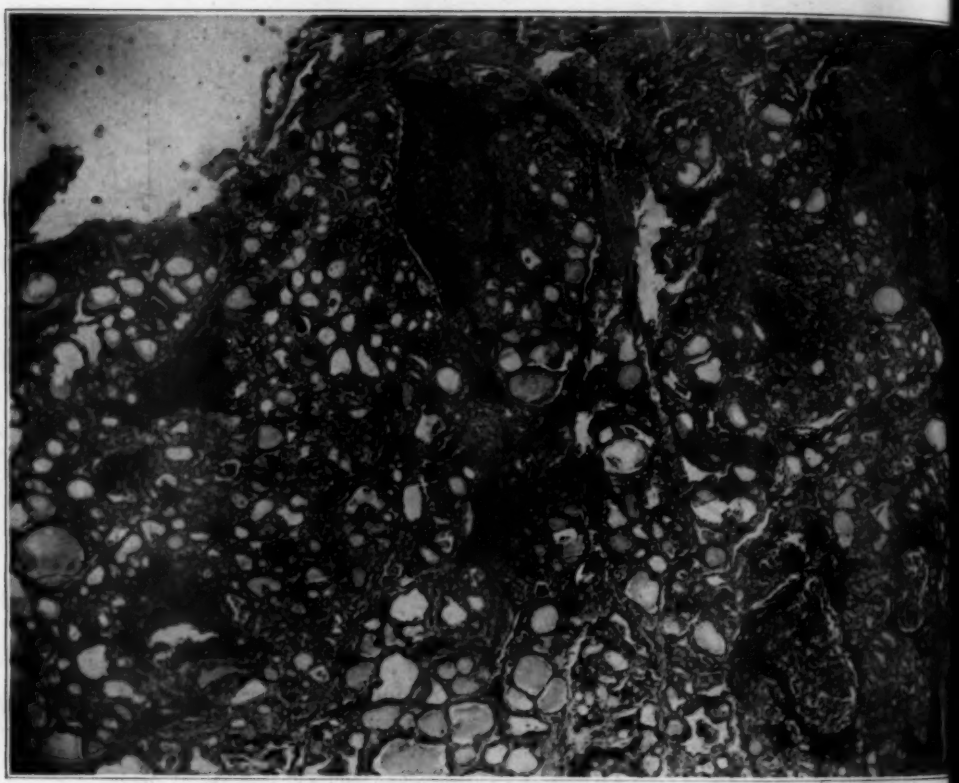

Fig. 2.—A low magnification of the removed thyroid tissue. The outstanding characteristic is the widespread lymphoid infiltration, with several lymph follicles. This could be seen in every microscopic field, the germinal centers being large and clear, with streams of lymphoid cells emanating from them and by their sinus paths delimiting entire gland units. One such glandular unit is clearly seen in the top center. Irregular aggregates of lymphoid tissue may be seen throughout the gland. Fibrosis is not a conspicuous feature; reduced from a magnification of × 27.

During the subsequent four days of rest and preoperative preparation further laboratory examination revealed: red blood cells, 4,750,000; hemoglobin, 98 per cent; white blood cells, 7,050; lymphocytes, 31 per cent; transitionals, 4 per cent; eosinophils, 2 per cent, and neutrophils, 63 per cent; coagulation time, five minutes;

bleeding time, two minutes; Wassermann reaction (Meinicke's modification), negative, and blood cholesterol, 195 mg. per hundred cubic centimeters of blood, the determination for cholesterol being made at the New Jersey College of Pharmacy, Newark, N. J.

On September 28, I performed a subtotal thyroidectomy. The operation was begun at 8:30 a. m. and closed at 10:10 a. m. Local anesthesia and ethylene and oxygen were used, the latter being administered by Dr. H. M. Stein. The gland was not adherent to the surrounding structures. A prominent pyramidal lobe was noted. The lack of hemorrhage was commented on, a feature I subsequently found

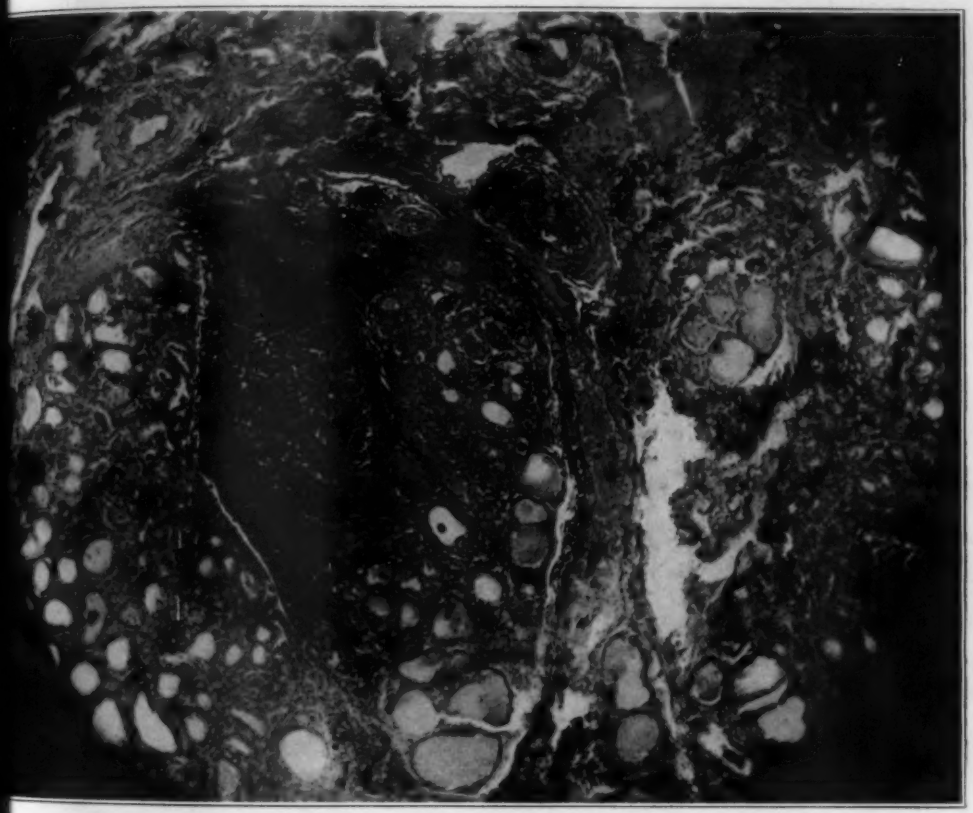

Fig. 3.—Higher magnification of the gland unit seen at the top center of figure 2. A large lymph follicle with a germinal center is seen at the hilus of the gland unit, with lymphoid tissue streaming away through the lymph channels which delimit the gland. Within the gland unit the lymphoid tissue has claimed most of the fields, thus impairing the thyrogenous function of the follicles within the gland unit, so that the colloid is much diminished or entirely absent; reduced from a magnification of × 54.

to have been observed by other authors when operating on thyroid glands with a similar pathologic process. About one half to three fourths of the right lobe, the lower portion of the isthmus and pyramidal lobe and about one half the left lobe were resected (fig. 1).

The pathologic observations as reported by the pathologist, Dr. H. Wassing, were as follows: There were two specimens, one from the right and one from the left lobe of the thyroid gland, each the size of a prune. The surface was smooth, showing the thyroid capsule except for the part along which the resection was per-

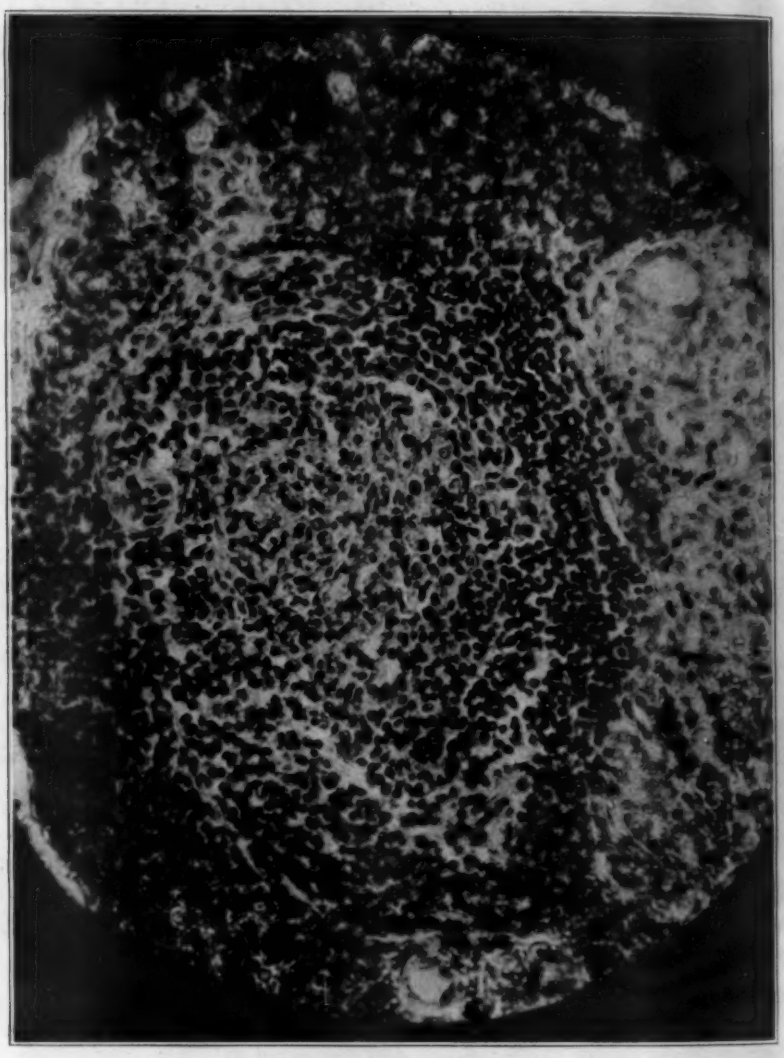

Fig. 4.—Oil immersion of the germinal center in the lymph follicle at the hilus of the gland unit shown in figure 3. Cells undergoing active mitosis may be picked out here and there in the center of the field; reduced from a magnification of × 243.

formed. There and on other cross-sections a diffuse, finely granular surface was seen, apparently poor in colloid; there were many whitish opaque small foci, like lymph follicles. On microscopic examination one saw hypertrophic (toxic) struma, with

many areas in which colloid was absent and in which there were relatively larger, cuboidal or polyhedral follicular cells; a few areas showed an attempt at formation of folds of the epithelium. The outstanding feature was the enormous lymphoid infiltration, with several lymph follicles in every field, with large germinal centers; there also were a few areas in which the lymphoid tissue seemed to be diffusely infiltrating, but there was no evidence of true lymphogranuloma.

Except for an immediate crisis of moderate severity the postoperative course was uneventful. The patient left the hospital on October 6. On that day the

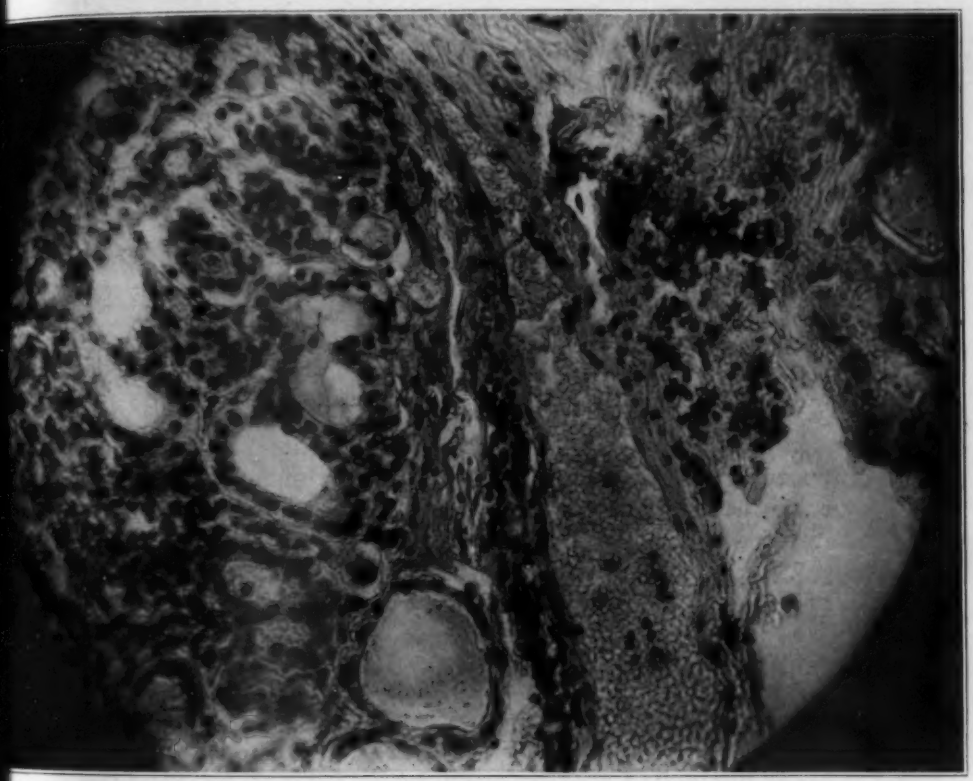

Fig. 5.—Oil immersion of the lymph sinus and blood capillary delimiting the right edge of the gland unit shown in figure 3. Several aggregates of lymphoid tissue may be seen in the blood capillary. Toward the lower edge of the photomicrograph is a lymph cell in the act of squeezing through the capillary wall, thus effecting its escape from the lymph sinus; reduced from a magnification of × 243.

basal metabolic rate was plus 26, the pulse rate 100, the blood pressure 164 systolic and 100 diastolic and the weight 115 pounds. There was a marked decrease in hidrosis.

On November 25, the basal metabolic rate was plus 35, the pulse rate 120, the blood pressure 200 systolic and 120 diastolic and the weight 119.5 pounds (54.3 Kg.). The nocturnal hyperhidrosis complained of preoperatively had disappeared. The administration of compound solution of iodine appeared to make the patient

perspire. I discontinued the use of iodine, and the patient became free from this annoying symptom. I cannot account for the persistent elevation of the basal metabolic rate and pulse rate and the hypertension. The patient stated that she felt better than before, and she gained weight. The last-mentioned weight is more than she ever weighed.

PROGNOSIS

Joll [5] stated that myxedema is the ultimate clinical feature, though it failed to develop in one case he observed for years. He stated that myxedema quickly follows resection of the gland. Williamson and his associates [2] stated that progressive symptoms rarely appear before the age of 45, while myxedema occurs on an average of a decade later. They performed a necropsy on a man, aged 65, whose thyroid gland exhibited early struma lymphomatosa and whose history disclosed no coexisting myxedema.

TREATMENT

It is too soon to judge, on the basis of this one case, the efficacy of thyroidectomy during the early stage of struma lymphomatosa associated with hyperthyroidism. Thus far the patient is definitely improved. In the light of McCarrison's experimental work on rats, previously mentioned, prophylaxis in the form of a diet rich in vitamins seems advisable. Iodine appears not to be helpful. Furthermore, it is obvious that in the present state of knowledge a preoperative diagnosis of struma lymphomatosa associated with hyperthyroidism cannot be made. However, in the later stages of the disease Joll and his associates believed that a diagnosis can be made, especially when in association with hypothyroidism. When so made, thyroidectomy is contraindicated unless the pressure on the trachea interferes greatly with the patient's activities. Joll suggested the administration of dried thyroid gland as a postoperative therapeutic measure, with regular check-ups on the basal metabolic rate as a guide.

COMMENT

It is well known that in exophthalmic goiter the thyroid gland is frequently invaded by lymphoid tissue, with definite lymphoid nodules often found scattered through the gland. Usually associated with such a change there is local and distant lymphadenitis, even the lymph nodules in the intestine being involved (MacCallum [8]). There is also associated distinct lymphocytosis. But the outstanding pathologic change in exophthalmic goiter is the reduplication of epithelium, the lymphoid invasion of the gland being only a secondary microscopic observation and quantitatively usually negligible. The pathologic picture in struma lymphomatosa associated with hyperthyroidism as found in my

8. MacCallum, W. G.: A Text-Book of Pathology, ed. 2, Philadelphia, W. B. Saunders Company, 1922, p. 881.

case presents a striking contrast. Both macroscopically and microscopically (figs. 1 to 5) the lymphoid invasion of the gland was the outstanding pathologic change. This was not associated with local or distant lymphadenitis; it was not associated with distinct lymphocytosis, and there was no reduplication of follicular epithelium.

SUMMARY

I believe this to be the first case of struma lymphomatosa associated with hyperthyroidism to be reported. As such it furnishes an important link in the pathogenesis of struma lymphomatosa when associated with no thyroid or hypothyroid symptoms. The clinical and pathologic features are described and treatment suggested.

CONCLUSIONS

1. Struma lymphomatosa (Hashimoto) is a distinct pathologic entity of rare incidence. 2. Thyroidectomy is indicated when the condition is associated with hyperthyroidism or when it is associated with symptoms referable to compression of the trachea. 3. Thyroidectomy is contraindicated when the condition is associated with no thyroid symptoms or hypothyroidism.

CARTILAGINOUS EXOSTOSIS OF THE SCAPULA

REPORT OF TWO CASES

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AND
BÉLA HALPERT, M.D.
NEW HAVEN, CONN.

Osseous growths capped by a layer of hyaline cartilage frequently occur about the epiphyses of long bones but also occasionally in flat bones. They are usually multiple and are believed to originate from misplaced islets of epiphyseal cartilage and thus appear during skeletal development and cease growing when the latter is completed. A solitary cartilaginous exostosis of the scapula with no growths elsewhere is rare. A review of the available literature yielded records of less than twenty instances. In this article two cases recently observed in the New Haven Hospital are reported.

REPORT OF CASES

CASE 1.—A Negro boy aged 7 years was admitted to the New Haven Hospital on March 13, 1928, with the complaint of prominence of the left scapular region. According to the mother this was first noted when the child was 4 years old. Since then the deformity has increased slightly and caused some pain occasionally but no apparent interference with the motions of the shoulder. A history of rickets, tuberculosis or syphilis was not obtained. The family history was not contributory; six brothers and three sisters were living and well. On admission the child appeared to be healthy, well developed and well nourished, presenting nothing unusual except the prominence of the left scapular region. The inferior angle appeared elevated, projecting posteriorly about 2 cm. above the level of the right scapula. Attached to the costal surface of the inferior angle, a firm, irregular mass, the size of a golf ball, was felt. This mass was not tender or painful and did not interfere except with the extreme motions of the shoulder. Roentgenographic examination revealed a deformity of the lower third of the left scapula suggesting a bony prominence. A diagnosis of osteochondroma of the left scapula was made, and on March 16, the infrascapular portion of the shoulder blade together with the tumor was removed by Dr. Winthrop M. Phelps.[1]

The resected portion of the scapula was triangular and measured 5.5 by 5.5 by 5 cm. Attached to its anterior surface was a somewhat nodular bony prominence shaped like a mushroom, the head of which was covered with cartilage and measured from 3.5 to 4 cm.; the stem was from 2.5 to 3 cm. in diameter. Cartilaginous and tendinous tabs were attached to the stem. A sagittal sawcut through the midportion of the specimen showed that it consisted of cancellous bone rimmed by a narrow zone of compact bone. In an area 1 cm. in diameter the

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From the Department of Pathology and the Department of Surgery, Yale University School of Medicine.

1. Phelps, Winthrop M.: A Method of Resection of the Infra-Spinous Portion of the Scapula Without Impairment of Shoulder Muscle Function, Yale J. Biol. & Med. **2**:39, 1929.

central portion contained soft marrow. A microscopic preparation of the entire sagittal section (fig. 1) showed well formed cancellous bone rimmed on the sides by a narrow zone of compact bone and capped by a layer of hyaline cartilage. The latter merged in a perfectly regular manner with the underlying cancellous bone. No bony lamellae were present in the central portion of the elevation, and the space was filled with bone marrow. At the base the cancellous bone merged with the scapula.

The patient made an uneventful recovery and was discharged on April 2, 1928. When he was seen one year later there was no limitation of motion or weakness

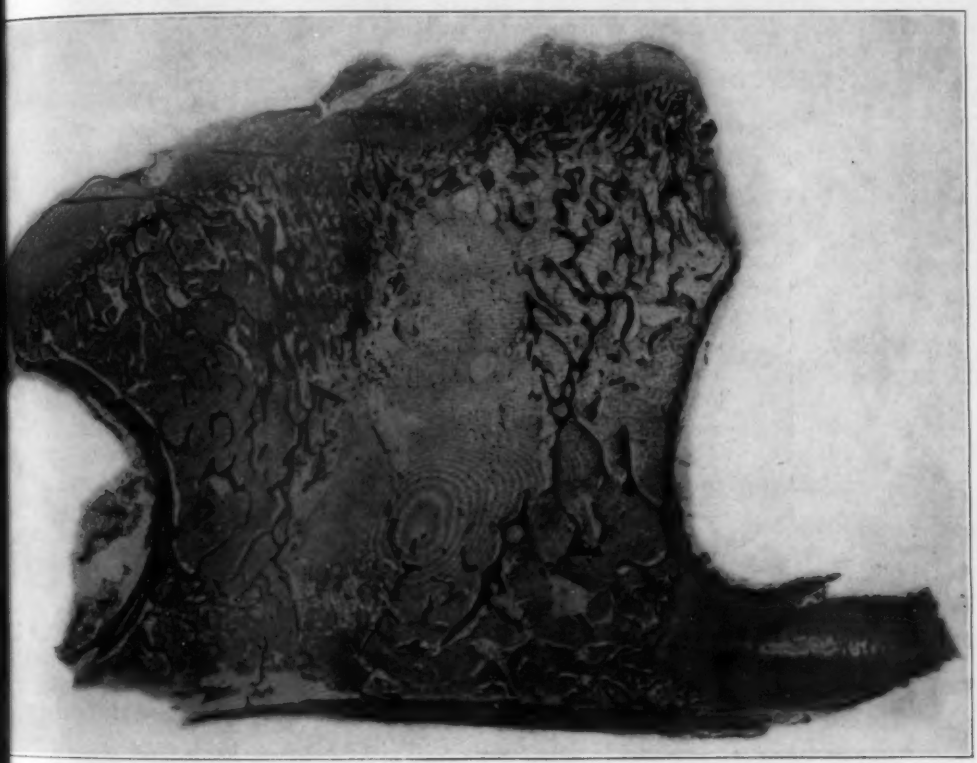

Fig. 1.—Microscopic preparation of a sagittal section through the midportion of a cartilaginous exostosis of the scapula in a 7 year old Negro boy; × 3. The growth consists of cancellous bone rimmed on the sides by a narrow zone of compact bone and capped by a layer of hyaline cartilage.

of action in any of the muscles of the shoulder. Three years later there had been no recurrence of the growth.

Case 2.—A girl aged 16 years was admitted to the New Haven Hospital on Sept. 11, 1933, complaining of a painful tender growth on the back of her right shoulder, which had been present for over three years. When first noted the deformity was thought to be due to bad posture. The growth increased slowly and was accompanied by a dull aching pain and tenderness, but caused no limitation of the movements of the shoulder. The past and family histories were noncontributory. Two brothers and two sisters were living and well.

On admission the patient appeared well developed and well nourished, and except for the prominence of the right scapular region, presented no abnormality. At about the medial angle of the scapula there was a bony prominence the size of a "small orange" projecting toward the ribs. There was a grating on motion of the scapula, but no limitation of movements. Roentgenographic examination revealed a bony prominence with a cancellous structure attached to the subscapular surface of the scapula near the medial angle. A diagnosis of exostosis of the scapula was made, and on September 12 the medial angle of the scapula together with the attached growth was resected by Dr. Samuel C. Harvey.

The removed portion of the scapula measured 5.5 by 3 by 1 cm. Attached to its concave surface was a mushroom-shaped bony spur capped by cartilage. The head measured 2.5 by 1.5 cm. in diameter; the stem was 1.7 cm. thick. The spur projected 2 cm. above the surface of the scapula. A sagittal sawcut showed the

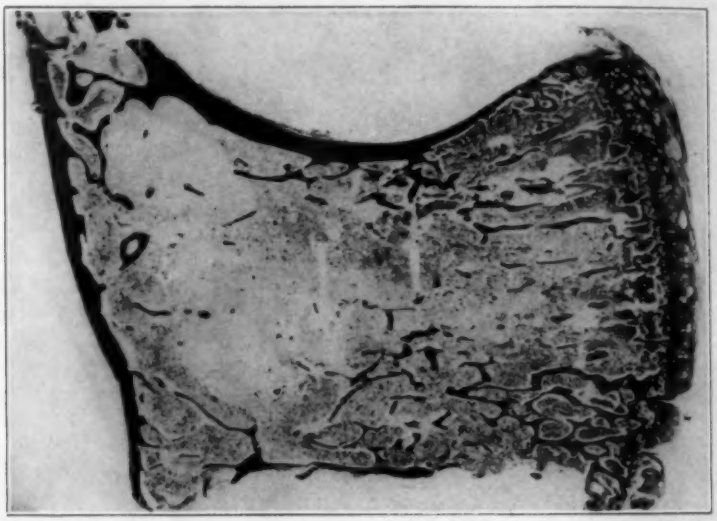

Fig. 2.—Microscopic preparation of a sagittal section through the midportion of a cartilaginous exostosis of the scapula in a 16 year old girl; × 3. The growth consists of cancellous bone with well formed lamellae and marrow spaces bordered by a thin layer of compact bone on the sides and covered on the free surface by a layer of hyaline cartilage.

spur to be composed of cancellous bone covered on the sides by compact bone, merging with the scapula at its base and covered by cartilage on the opposite surface. A microscopic preparation of the spur (fig. 2) showed cancellous bone with well formed lamellae and marrow spaces bordered by a thin layer of compact bone on either side. The spur continued into the scapula at the base. The opposite surface was covered by a layer of hyaline cartilage. Along the chondro-osseous junction which was fairly straight there was a suggestion of formation of new bone.

The patient was discharged on the seventh day (September 19) following the operation. When seen four months later she had no complaints and no impairment in function of her shoulder.

REPORT OF CASES FROM THE LITERATURE

BEAUMONT.—The first case of cartilaginous exostosis of the scapula was reported by Beaumont [2] in 1838. A boy aged 13 years was seen "on account of a very considerable projection of the inferior angle of the right scapula, attended with pain after exertion, loss of power, and diminished freedom of motion in the right upper extremity." Recently the tumor had increased in size and "the patient began to be incapable of following his occupation, in which he was frequently obliged to lift and carry parcels of considerable weight." The inferior angle of the scapula was "thrown out from the ribs nearly two inches above its level, which was caused by a tumor, the size of a large walnut" attached to the costal surface of the inferior angle of the scapula. On account of the hardness of the projecting portion and of its unyielding attachment to the scapula it was thought to be an exostosis. On July 5, 1838, the tumor was removed, together with a portion of the scapula to which it was attached. The growth consisted of cancellous bone with areas of firmer osseous tissue; its entire free surface was covered by a thick layer of cartilage—"as hard and compact as articular cartilage." Between nine and ten weeks after the operation the patient was "free from pain, and his right arm had become as strong as the other and possessed the same extent and freedom of motion"—and "for two weeks past he resumed his former occupation."

PEPPER.—The second case of cartilaginous exostosis of the scapula was presented before the Pathological Society of Philadelphia on Oct. 24, 1867, by George Pepper.[3] A specimen removed at necropsy of a 16 year old colored boy who died of tuberculosis was shown. Prominence of the right scapula had been noted during life though it had caused no symptoms. "The growth sprang from the under surface of the bone, close to the posterior border, and about midway between the upper and lower angles." It had a mushroom-like appearance with a broad sessile attachment and thick overhanging edges. It measured 1½ by 1 inches (3.81 by 2.54 cm.) and was elevated about 1 inch above the surface of the bone, which seemed normal. On section the pedicle was seen to have an osseous structure; the body was partly osseous and partly calcareous, overlaid by a thin layer of cartilage. The gross observation was verified by microscopic examination.

BIRKETT.—In 1869 Birkett [4] mentioned in his presentation of cartilaginous and bony growth that he had seen three patients with exostoses of the scapula: "a boy twelve years of age, and two girls, one sixteen years old, the other twelve. In the first the growth had been observed four months, in the second three years, in the third one year. The tumors were small and do not require any particular description."

RICHET.—In 1885 Richet [5] removed an exostosis of the scapula from a boy 12 years old. The growth had been noted as a small swelling five or six years previously, and since that time it had not increased in size or caused any discomfort.

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2. Beaumont, William: Exostosis of Scapula, London M. Gaz. **23**:162, 1838.

3. Pepper, George: Osteo-Enchondroma of the Venter of the Right Scapula, Am. J. M. Sc. **55**:400, 1868.

4. Birkett, John: Cartilaginous and Bony Growths: Exostoses on the Bones of the Upper Extremity, Guy's Hosp. Rep. **14**:499, 1869.

5. Richet: Exostose de l'angle inférieur de l'omoplate, France médicale **32**: 460, 1885.

HEURTAUX.—In November 1885, at a meeting of the Société Anatomique de Nantes, Heurtaux [6] described a scapula with a cartilaginous exostosis removed from a man, 24 years old. The growth was attached to the spine of the scapula by a slender pedicle, had the form of a "coracoid process," and consisted of cancellous bone covered by a broad layer of hyaline cartilage.

VON KÖLLIKER.—In 1891 von Kölliker [7] reported two cases of "congenital upward displacement of the shoulder blade," ascribed to exostosis of the scapula. The first patient, a boy, aged 10 years, had an exostosis on the medial angle of the right scapula which caused an upward and lateral displacement of the latter and resulted in a "scoliosis cervico-dorsalis dextroconvexa." The second patient, a boy aged 4 years, had an exostosis somewhat lateral from the medial angle of the left scapula. The hook or finger-like projection extended about 2 cm. over the clavicle. This drew the scapula upward, and a dorsal scoliosis, convex to the left, developed. In neither case was there any limitation of movements. Operative treatment was refused by the parents of both children.

KÖNIG.—In 1893, in discussing Schlange's paper on upward displacement of the scapula, presented at the twenty-second congress of the Deutsche Gesellschaft für Chirurgie, König [8] reported the case of a 7 year old girl. One scapula was markedly displaced upward, and a loud cracking was heard on certain movements of the shoulder. The patient had marked scoliosis. An operation disclosed an exostosis attached to the scapula in such a manner that it touched the second rib and thus interfered with the movements of the extremity. The exostosis was removed in the belief that it was the cause of the upward displacement.

ROBINSON.—In 1899, Robinson [9] reported an exostosis of the scapula in a girl aged 9 years. She had had the swelling nearly all her life. There was no complaint of pain or of any inconvenience. The right scapula appeared "winged," its inferior angle being raised off the chest wall and displaced upward and outward. The vertical distance from the spine to the inferior angle was 1 inch (2.54 cm.) less than on the left side. Just above the inferior angle of the scapula a hard nodular tumor with a base 2 inches (5.08 cm.) across was attached to the vertebral border. It caused no limitation of movements. The tumor removed on June 28, 1898, "was a typical cancellous exostosis, with a very marked cartilaginous cap growing from the epiphyseal line between the scapula and its vertebral border, and was about the size of a tangerine orange." When the patient was seen three months later all muscular movements were "perfect."

IRIBARNE.—In 1900 Iribarne [10] reported the case of an 8 year old girl who was seen on June 18, 1898, on account of a growth in the left scapular region; this was first noted when she was 8 months old. Since then the growth had increased in size causing deformity and some limitation of certain movements. The head was

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6. Heurtaux, M.: Exostose de croissance de l'épine de l'omoplate, J. de méd. de l'ouest **20**:384, 1886.

7. von Kölliker, T.: Bemerkungen zum Aufsatze von Dr. Sprengel "Die angeborene Verschiebung des Schulterblattes nach oben," in diesem Archiv, Band 42, Heft 3, Arch. f. klin. Chir. **42**:925, 1891.

8. König: Verhandl. d. deutsch. Gesellsch. f. Chir. **22**:68, 1893.

9. Robinson, H. Betham: Exostosis of the Vertebral Border of the Scapula: Removal, Brit. M. J. **2**:963, 1899.

10. Iribarne, Joseph: Contribution à l'étude des exostoses ostéogéniques, Thèse de Paris, 1900.

tilted to the right; there was a slight scoliosis with the convexity to the left. The left shoulder was elevated, and the inferior angle of the left scapula was four fingerbreadths above that of the right. A triangular tumor was located on the posterior surface of the left scapula along the vertebral border at the middle of the lower third. It measured from 3 to 4 cm. in height. Movements were free except that elevation of the arm was arrested at less than 45 degrees. The tumor was thought to be an exostosis and was resected by Broca. Nine months following the operation the left scapula was still elevated.

GANTCHEFF.—In 1901 Gantcheff [11] reported an exostosis of the scapula in a 7 year old boy. A prominence in the region of the left scapula was first noted three months previously and was thought to be due to scoliosis. The deformity did not seem to increase. On examination there was no scoliosis. The vertebral border of the scapula was elevated owing to a bony tumor about 5 cm. in diameter at its base attached to the costal surface of the scapula near the vertebral border. The movements of the shoulder were not impaired. There was a suggestion of a slight osseous prominence in the region of the spine of the same scapula, but none elsewhere. The growth removed on June 7, 1900, measured 3 cm. in height, had the shape of a "champagne bottle," and consisted of cancellous bone covered by cartilage.

FERBOS.—In the case reported by Ferbos,[12] in 1906, the patient was under Guyot's care. A girl aged 15 years complained of a deformity of the right scapular region, which had been present for several years. No history of trauma was obtained. The father and mother, two brothers and two sisters were living and well. Attached to the scapula on the vertebral border a firm elevation about 4 by 5 cm. was noted. This scapula measured 1 cm. less in the horizontal and vertical directions than the normal left scapula. A diagnosis of exostosis of the scapula was made, and the tumor was removed two months following the first examination. The specimen consisted of a bony spur, with the free surface covered by a bursa. The peripheral portions were dense, the central portion spongy, with no medullary cavity. The patient made a good recovery, and when she was seen ten months following the operation there was no pain or recurrence of the growth.

MCWILLIAMS.—In 1914, McWilliams [13] reported the following case: A girl aged 18 years complained of dull aching pains in the left shoulder and of a grating or creaking sound on drawing the scapula backward and forward; the condition had been present for one year. The patient stated that twelve years previously, following a fall, the left scapula began to become prominent. For this condition she wore a brace for a year without any benefit. A swelling was noted just inside the scapula. On examination the left scapula was prominent with a fulness at the lower part where an indefinite swelling about the size of a lemon was felt which extended forward beneath the scapula. A roentgenogram showed an "exostosis on the inner side of the lower part of the left scapula." At operation the growth seemed to be partially surrounded by a bursa. The specimen removed was about 4 cm. long, with a broad oval end covered by cartilage and a narrow pedicle by which it was attached to the scapula. Microscopic examination showed the growth

11. Gantcheff, Georges: Etude sur les exostoses de l'omoplate, Thèse de Lyon, 1900-1901, no. 163.

12. Ferbos, H.: Des exostoses de l'omoplate, Thèse de Bordeaux, 1906.

13. McWilliams, Clarence A.: Subscapular Exostosis with Adventitious Bursa, J. A. M. A. **63**:1473 (Oct. 24) 1914.

to be composed partly of bone and partly of cartilage. Two months following the operation the appearance of the shoulder and the position of the scapula appeared normal, and there was no pain on motion.

PEAK.—In 1914, Peak [14] reported the case of a girl aged 7 years whose mother noted that for the previous three years the child's right shoulder blade seemed to increase in size. The tumor was attached to the costal surface about midway between the lower angle and the spine. Microscopic examination of the removed growth showed it to be an "osteo-enchondroma."

BROWN.—In 1916, Brown [15] reported a case of cartilaginous exostosis of the scapula in a 16 year old girl. She complained of prominence of the right shoulder, present for two or three years. The condition became more noticeable and painful a few weeks preceding the examination. No history of trauma was obtained. The right shoulder was prominent; crepitation could be elicited, and it was noted that at times the scapula in sliding over the ribs would "catch and jump from one rib to another." This was associated with pain. During the subsequent one and a half years the patient was treated with exercises and braces. Since these measures proved ineffective the upper part of the right scapular region was exposed, and the medial angle of the scapula was resected together with a "hook-like process of bone" attached to its anterior surface. The removed portion of the scapula showed a backward bend of the medial angle and a bony prominence, "a little over 3 cm. in length," on its anterior surface attached at right angles by a broad triangular base. The middle portion or shaft was also triangular but smaller than the base or the free rounded end which was covered by a "white glistening cartilage-like material." The specimen was not submitted to microscopic examination. The patient made an uneventful recovery, and when seen five months following the operation she was "perfectly well as far as the shoulder was concerned."

GÉNÉVRIER.—In 1923, Génévrier [16] presented before the Société de Pédiatrie de Paris a case of exostosis of the scapula. The patient, a boy, aged 12 years, had a growth the size of a "mandarine" which was attached to the vertebral border of the right scapula. The growth was known to exist by the parents and the boy, but no attention was given to it. It caused no symptoms. It was incidentally discovered when roentgenograms of the chest were taken for a condition of the bronchi.

COMMENT

A cartilaginous exostosis is an osteochondroma—a benign neoplasm—in which the tissue components reproduce their normal structures and retain their orderly relations. Growth occurs in them at the chondro-osseous junction by endochondral formation of bone. The growth apparently occurs with equal frequency on either scapula of males or females. The location is on the vertebral border near the inferior angle or about other junctions of centers of ossification. This and the

14. Peak, I. Hunter: Osteo-Enchondroma of the Scapula, Kentucky M. J. **12**:800, 1914.

15. Brown, Lloyd T.: An Unusual Exostosis of the Scapula, Boston M. & S. J. **174**:652, 1916.

16. Génévrier, M.: Exostose de l'omoplate, Bull. Soc. de pédiat. de Paris **21**:47, 1923.

fact that the tumors behave like the exostoses of long bones support the view that they arise from accessory centers of ossification.

SUMMARY

Two cases of cartilaginous exostosis of the scapula with no growths elsewhere are presented, and similar cases gathered from the literature are reviewed.

INFLUENCE OF A DIET RICH IN CASEIN ON THE STRENGTH OF BONE AND THE HEALING OF FRACTURES

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It has become increasingly evident from our studies on the rat that the beam strength of the fibula varies in general with the body weight. When, for example, we plotted the strength of the fibulas of normal rats selected at random as a function of their body weight, the strength of the bones increased as the weight increased.[1] Again, when we started rats of approximately the same age on a diet on which it happened that they lost weight because they progressively ate less, their fibulas lost strength likewise.[2] It seems, therefore, that there is a definite strength of bone per unit of body weight, and that the strength of the weight-bearing bones varies directly with function (Wolff's law).

In spite of this general relationship between the strength of bone and the body weight, however, the ratio of the one to the other can be altered experimentally. The food ingested naturally influences the strength of bone by changing the body weight and changing the function of weight bearing, but undoubtedly it also influences the strength of bone directly. Burnett,[3] for example, fed hogs on a diet rich in tankage or bone meal and obtained an increase in the size and strength of bones out of proportion to the gain in body weight. The bones of the control animals fed alfalfa did not exhibit these changes.

The skeleton is the storehouse for the ingested mineral salts, and not a static mass of these salts in an inorganic matrix. Its calcium

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1. Lindsay, M. K., and Howes, E. L.: J. Bone & Joint Surg. **13**:491 (July) 1931.

2. McKeown, R. M.; Lindsay, M. K.; Harvey, S. C., and Howes, E. L.: The Breaking Strength of Healing Fractured Fibulae of Rats: II. Observations on a Standard Diet, Arch. Surg. **24**:458 (March) 1932.

3. Burnett, E. A.: Twenty-Fourth Annual Report of Agricultural Experiment Station, University of Nebraska, 1911, p. 178.

and phosphorus ions are in chemical equilibrium with similar ions of the blood. The direction of the flow of calcium salts in this blood-bone system depends on the supply of calcium and phosphorus and the solubility of these salts in the plasma.[4] Calcium salts can be withdrawn from bone when acids or parathyroid extract-Collip are given by mouth, and Bauer, Aub and Albright [5] have even demonstrated that the bony trabeculae are the readily available sources of calcium and phosphorus. Conversely, calcium can be deposited in bone by a diet rich in mineral salts or viosterol. Moreover, these fluctuations in the mineral salts of bone cause variations in their strength. For example, when the fibula is depleted of mineral salts either by immersion in an acid or by maintaining the animal on a diet low in salt, strength is lost.

The question naturally arises, then, whether the strength of bone and the healing of a fracture can be affected by changing of substances in the diet which affect the metabolism of the mineral salts. The calcium salts in the blood plasma occur in a supersaturated state, and this supersaturation has been attributed by Pryde to the fixation of both calcium and phosphorus ions in nondiffusible form by the proteins of the plasma.[6] These three constituents even have a mathematical relationship to one another. Peters and Eiserson found that the calcium in the blood serum varies directly with the concentration of protein and inversely with the concentration of inorganic phosphorus according to the formula, calcium $= -0.255$ phosphorus $+ 0.566$ protein $+ 7$. With such a balanced relationship, if it were possible to increase the amount of protein in the blood stream, there should be either an increase in the amount of calcium or a decrease in the amount of phosphorus, and a change in the ratio of bone strength to body weight. Actually, however, an excess of ingested protein is excreted as urea, and the blood remains chemically constant. It is the function of the blood stream to maintain constancy, and analyses of it do not indicate that more amino-acids have passed through it after the ingestion of a diet rich in protein than when this excess is not ingested. Likewise, the chemical constancy of the blood gives no idea as to whether the mineral salts are being carried from the gastro-intestinal tract to the skeleton or from the skeleton to the excretory channels. Variations in the strength of the bones should indicate, however, whether calcium salts have been deposited in the bones or removed from them, and we therefore felt justified in trying to change the strength of bone by a diet rich in protein.

4. Peters, J. E., and Eiserson, L. J.: J. Biol. Chem. **84**:155 (Oct.) 1929.

5. Bauer, W.; Aub, J. C., and Albright, F.: J. Exper. Med. **49**:145 (Jan.) 1929.

6. Pryde, John: Recent Advances in Biochemistry, Philadelphia, P. Blakiston's Son & Co., 1928.

EXPERIMENTATION

The diet rich in protein consisted of 80 per cent of casein with sufficient vitamins and salts to give it adequacy (table 1). Its caloric content is somewhat lower than the standard diet fed to the control animals.

Rats weighing from 190 to 300 Gm. and approximately 6 months of age were used. The animals had grown normally since birth. They were kept in separate cages and put on the diets one week before the experiment was started. They were allowed to eat all they wished, and their weights were recorded throughout the experiments. The animals were divided into two groups on each diet. One group was placed on the diets in order to determine their effects on the strength

TABLE 1.—*Standard Diet*

Percentage Composition	Per Cent	Calories per Kilogram of Food	Apportionment of Total Calories	Per Cent
Standard Balanced Diet				
Casein	18	738	Protein	13.8
Starch	51	2,091	Carbohydrate	39.2
Hydrogenated oil	22	2,046	Fat	47.0
Cod liver oil	5	465		
Salts (Mendel and Osborne mixture*)	4	5,340		
High Protein Diet				
Casein	80	3,280	Protein	68.7
Hydrogenated oil	12	1,488	Fat	31.8
Cod liver oil	4			
Salts	4	4,768		
On both diets: Lettuce twice a week, 70 mg. of yeast daily				

* The salt mixture consists of the following: calcium carbonate, 134.8 Gm.; magnesium carbonate, 24.2 Gm.; sodium carbonate, 34.2 Gm.; potassium carbonate, 141.3 Gm.; phosphoric acid, U.S.P., 103.2 Gm.; hydrochloric acid, 53.4 Gm.; sulphuric acid, 9.2 Gm.; citric acid plus water, 111.1 Gm.; crystallized iron citrate, 6.34 Gm.; potassium iodide, 0.020 Gm.; manganous sulphate, 0.079 Gm.; sodium fluoride, 0.248 Gm., and potassium aluminum sulphate, 0.0245 Gm.

of bone, and the right fibulas of the other group were fractured in order to study the effects of the diets on the healing process. The fractures were made by cutting the fibulas at their midpoints with scissors, and the fragments were left in the best possible alinement. The technic for this procedure has been described before.[1] At intervals of three days from the sixth to the fifty-fourth day five animals were killed from both groups on both diets. The soft parts were stripped from the fibulas, and the bones were fastened together in pairs with a tag bearing the body weight. After they were dried in a desiccator for one week, their strengths were determined on a testing apparatus devised for the purpose.[1] The apparatus consists of two supports across which the bone is suspended. The supports are mounted on the pan of a scale balance. With the bone in place, the breaking force is applied at a constant rate at two points equidistant from the support. The strengths of five tests were averaged for each interval and plotted as a function of time.

Roentgenograms were taken of typical calluses at each three day interval, and cross-sections of each were measured and examined with a binocular microscope.

RESULTS AND COMPARISON OF CURVES

Normal Fibula.—The body weight and the strength of the fibulas are given in table 2.

The ratios of the body weight to the strength of the fibulas are plotted in figure 1. Those for the rats on the diet rich in casein fluctuate

TABLE 2.—*Strength of Normal Fibulas and Body Weight*

	Standard Diet			Diet Rich in Casein		
Experimental Days	Weight at Death	Left	Right	Weight at Death	Left	Right
6	261	643	606	224	291	293
9	294	509	484	209	480	438
12	226	415	439	239	532	475
15	204	306	308	236	530	573
18	196	289	279	260	566	498
21	232	403	339	213	501	511
24	232	500	555	252	491	418
27	212	490	458	211	413	383
30	221	306	356	244	604	556
33	205	268	294	216	520	505
36	201	321	266	246	860	744
39	225	393	368	258	468	403
42	211	415	420	245	840	771
45	208	434	416	215	379	384
Averages	223.4	415.1	399.3	233.4	583.9	496.6
Ratio		1.85	1.50		2.28	2.10

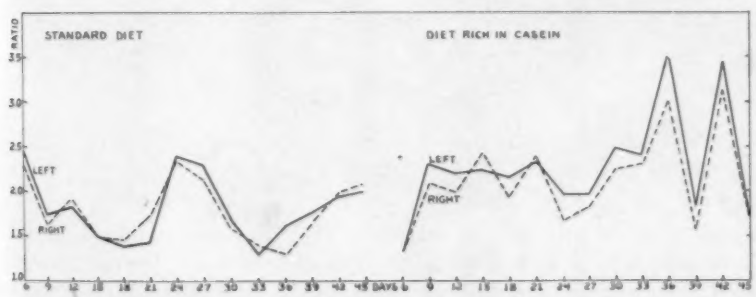

Fig. 1.—Ratio of the body weight to the strength of the fibulas of animals fed the standard diet and those fed a diet rich in casein.

like those for the rats on the standard diet, but they are in general greater. The strength of the fibula, therefore, has been increased in proportion to the body weight by the ingestion of the diet rich in casein.

Fractured Fibula.—The breaking strength of the healing fractures and of the opposite uninjured fibulas is given in table 3. The curves of the ratios of these to the body weights are given in figure 2.

In the previous publications we described the curve of the healing strength of the fractured fibula of the adult rat fed on the standard

diet. This curve had four distinct phases corresponding to the anatomic changes taking place during healing. In the first phase of fibrinous and early fibrous union, from the first to the sixth day, the callus had no strength. In the second, until the fifteenth or twentieth day, there was a rapid increase in its strength as the late fibrous union progressed and the "primary callus" was deposited. During the subsequent interval, or the third phase, the strength decreased as the callus organized.

TABLE 3.—*Strength of Fractured Fibulas and Opposite Uninjured Fibulas*

Postoperative Days	Standard Diet		Diet Rich in Casein	
	Left	Right	Left	Right
6	464	57	318	51
9	464	217	339	231
12	505	283	414	247
15	625	401	371	217
18	428	261	475	263
21	326	244	417	217
24	457	269	385	304
27	418	283	279	254
30	359	302	378	310
33	413	295	561	286
36	539	353	510	413
39	530	349	382	333
42	366	311		
45	463	441		

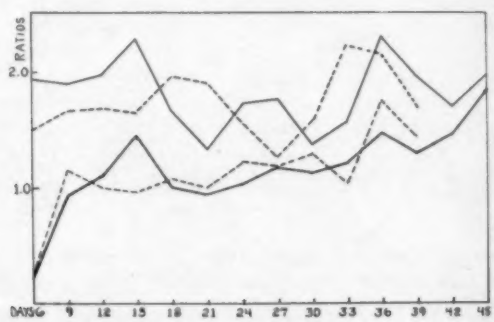

Fig. 2.—The ratio of the strength of the right and left fibulas to the body weight of animals fed the standard diet is represented by the solid line; that of animals fed a diet rich in casein, by the dotted line. The two upper curves are for the left uninjured fibulas; the lower two for the right fractured fibulas.

Finally, however, as organization was completed and the cortex reformed and realinement of the fragments took place, there was again an increase in strength. At the end-point the ultimate strength of the callus was greater than that of the rest of the bone, although until this point was reached the callus had broken, except in a few isolated instances, when

apparently some weakness in the rest of the bone had caused the break to occur elsewhere. The end-point occurred on the forty-fifth day.[7]

On this diet rich in casein, the curve of the ratios is quite different from that obtained for the standard diet. The end-point is reached on the thirty-ninth day, a shortening of six days, and the initial rise is more rapid, although its peak is not so high. Consequently, the subsequent loss is not so great. From the eighteenth day on, the curve steadily mounts in strength approximately at the same rate as the standard curve. It is of interest to note also that the curves for the diet high in protein exhibit a parallelism between the strength of the right and that of the

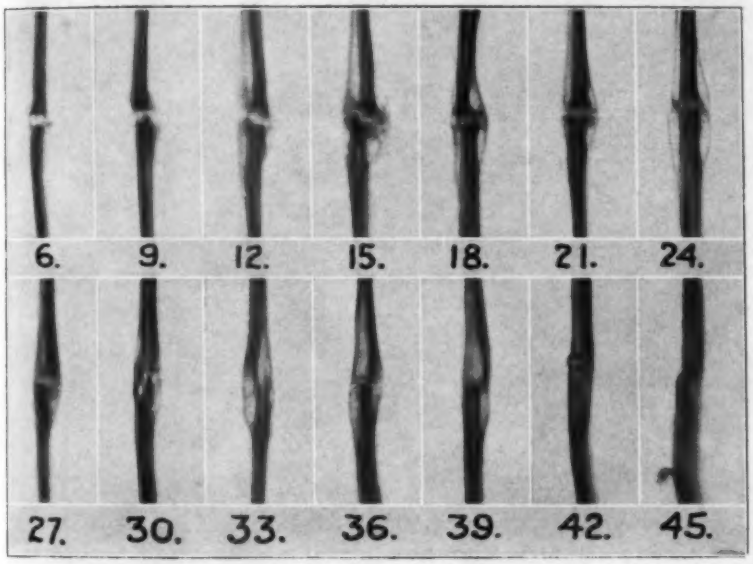

Fig. 3.—Roentgenograms of typical fractures at three day intervals from the sixth to the forty-fifth postoperative day. The animals were fed the standard diet. Note the haziness of the ends of the fractured fragments after the thirtieth day.

left fibula only after the twenty-seventh day, while in the standard curve parallelism of the ratios was present practically throughout.

Studies of the roentgenograms of the calluses of the animals fed on the diet high in protein showed that the ends of the fractured fragments could be identified as separate entities for a much longer period than they could be in the controls (figs. 3 and 4). Gross examination of the calluses also revealed the same persistency of the identity of the

7. Subsequent work since this article was submitted for publication has shown that after the forty-fifth day there is again a period when the breaks occur at the site of fracture.

fragments in the bones of animals fed on the diet rich in casein. The measurements of the external diameters of the calluses were practically the same for both groups.

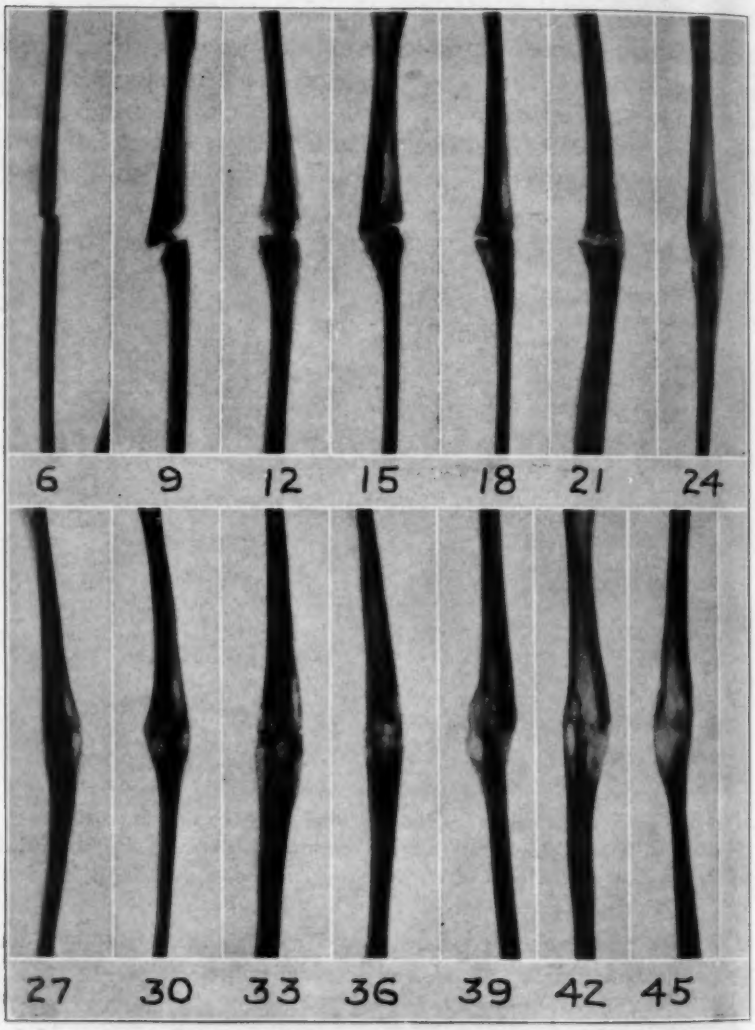

Fig. 4.—Roentgenograms of typical fractures of animals fed a diet rich in casein. Note the distinctness of the ends of the fractured fragments even until the forty-second day.

COMMENT

The data suggest that a diet rich in casein strengthens normal bone and speeds the healing fractures. Our first thought in using this diet was that the increase in the amount of casein simply increased the

protein content of the diet. However, it soon became apparent that increasing the casein also increased the salt and vitamin content of the diet. The animals were therefore ingesting a greater quantity of three elements which could strengthen bone and hasten healing. All three would also provide greater availability of the calcium salts. That there was greater availability of the calcium salts is attested by the increase in strength of the normal fibulas and the more rapid rate of healing. In addition, there was some substantiation for the greater availability of calcium salts found in the behavior of the fractured fragments. Axhausen [8] believed that the absorption of the ends of the fractured fragments during healing made available a local source of calcium. On the diet rich in casein this absorption was not so apparent either by gross or by roentgen examination, suggesting that the calcium obtained from the fragments was not needed.

Not all of the rapidity of the initial rise of the curve of healing on the diet rich in casein can be attributed to the greater availability of calcium salts, however. Part of it undoubtedly must be from the stimulation of fibrous proliferation by the diet high in protein. Harvey and Howes [9] have shown that wounds of soft tissues have a greater rate of fibroplasia on a diet high in protein. This stimulation alone might account for the changed contour of the first two periods of the curve.

CONCLUSIONS

1. A diet rich in casein increased the strength of bone per unit of body weight in rats.

2. A diet rich in casein accelerated the rate of healing of fractures.

8. Axhausen: Verhandl. d. deutsch. path. Gesellsch. **16**:309, 1913.

9. Harvey, S. C., and Howes, E. L.: Ann. Surg. **91**:641 (May) 1930.

TREATMENT OF VARICOSITIES

PRELIMINARY HIGH LIGATION OF THE INTERNAL SAPHENOUS VEIN WITH THE INJECTION OF SCLEROSING SOLUTIONS

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In December 1928 the clinic for peripheral vascular conditions was organized at the Massachusetts General Hospital to study and direct the treatment of varicose veins and other circulatory disturbances of the extremities. Since the inception of the clinic the care of patients admitted to the hospital as well as those seen only in our outpatient department has been under the supervision of the same group of men, and thus my associates and I have been able to maintain a desirable degree of unity in the different phases of the work. By an interchange of individual ideas during the combined weekly house visit, when all of the members of the clinic are present, and by seeing for ourselves every patient who reports to the outpatient department, we have a favorable means of determining the outcome for all of the patients treated, whether they have been hospitalized or not. From the disappointing results of our earlier work in the treatment of varicose veins by the injection method alone [1] it was felt that the question of the efficacy, in certain cases, of combining preliminary high ligation of the internal saphenous vein with injections was a matter worthy of further study. The following report is based on our experience during the period from August 1931 to April 1933 in treating one hundred and seventeen patients by the combined method of ligation and injection. All of the members of our clinic have contributed suggestions as to methods of procedure and have participated in the actual work involved in caring for the patients, and the technic and principles set forth in the following pages represent the combined efforts of a group rather than the effort of any one person.

In many cases of varicose veins of the internal saphenous system it can be demonstrated that with the patient in the upright position the blood flow in the main trunk is reversed and the lower part of the leg subjected not only to the weight of this column of blood but to any increased intra-abdominal venous pressure occasioned by exertion, straining and similar forces. So clearly and convincingly was this fact

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From the clinic for peripheral vascular conditions, Massachusetts General Hospital.

1. Faxon, H. H.: End Results in the Injection Treatment of Varicose Veins, New England J. Med. **208**:357, 1933.

stated by Trendelenburg [2] that his work has remained a classic corroboration of an underlying principle which was recognized years before his time. Subsequent work with roentgenograms and injections of iodized poppy-seed oil [3] and direct manometer readings [4] have added so little that the Trendelenburg test is still our best guide for determining the competency of the valves in the main saphenous trunk above the knee. It would seem worth while to restate briefly the salient points of the test, as an understanding of its basic principles are of the first importance in any treatment of varicose veins.

The Trendelenburg test (fig. 1) is carried out by elevating the affected leg as the patient lies on the examining table to an angle of 45 degrees, thus essentially emptying the varicosities of blood. A tourniquet is then placed about the thigh

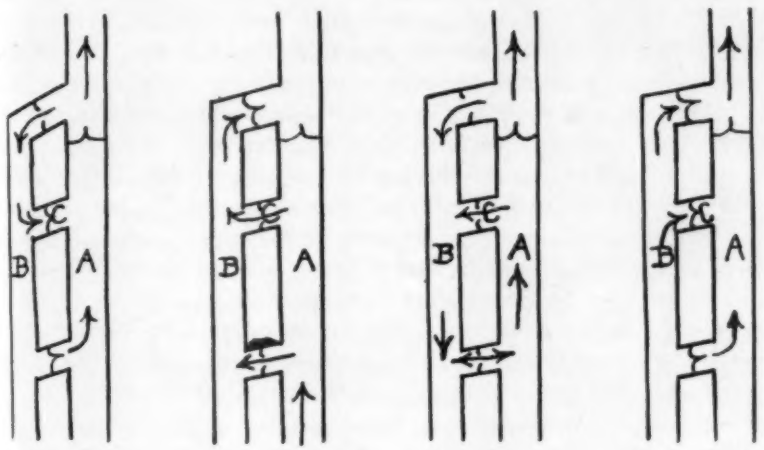

Fig. 1.—The four Trendelenburg states, according to Bernstein (*Acta chir. Scandinav.* **62**:66, 1927), as modified by McPheeters ("Varicose Veins," Philadelphia, F. A. Davis Company, 1931). *A* indicates the femoral vein; *B*, the internal saphenous vein, and *C*, the communicating vein.

tight enough to constrict only the superficial venous circulation, and the patient is allowed to stand with the tourniquet still in place. If the varicosities fill rapidly (i. e., within one-half minute) from below, incompetence of the valves in the branches communicating with the deep system is signified. A slow filling or no filling under these conditions means that the adequate functioning of the valves

2. Trendelenburg, F.: Ueber die Unterbindung der Vena saphena magna bei Unterschenkelvaricen, Beitr. z. clin. Chir. **7**:195, 1891.

3. McPheeters, H. O., and Rice, C. O.: Varicose Veins: Circulation and Direction of the Venous Flow, Surg., Gynec. & Obst. **40**:29, 1929.

4. de Takáts, G.; Quint, H.; Tillotson, B. I., and Crittenden, P. J.: Impairment of Circulation in the Varicose Extremity, Arch. Surg. **8**:671 (Feb.) 1929. McPheeters, H. O.; Merkert, C. E., and Lundblad, R. A.: The Mechanics of the Reverse Flow of Blood in Varicose Veins as Proved by Blood Pressure Readings, Surg., Gynec. & Obst. **55**:298, 1932.

is little, if at all, impaired. If the tourniquet is released with the patient still standing and a prompt engorgement of the internal saphenous trunk and its superficial branches ensues, it is evident that the valves in the main trunk of this system are incompetent to withstand the back pressure to which they are subjected. With incompetent valves in the communicating branches and the main trunk, filling occurs from below and is augmented from above when the constriction about the thigh is removed. From a study of the distribution of the prominent veins of the leg and a repetition of the test with the tourniquet applied a second time just below the popliteal space, varicosities of the external saphenous vein alone or a combination of a varicosed condition involving the external and internal systems may be properly evaluated.

With an understanding of the facts brought out by this test it is obvious that any effective treatment of varicosities of the internal saphenous system in which incompetence of the valves in the main trunk can be demonstrated must include some step to shut off the reverse flow of blood into this system. Trendelenburg [2] sought to secure this end by ligating the main saphenous trunk and recommended that this be done at the junction of the middle and lower thirds of the thigh. Later workers, including Mayo,[5] Miller [6] and Homans,[7] rightly felt that a higher point of ligation than that used by Trendelenburg would more effectively forestall recurrences by also removing from the upper portion of the main trunk the back pressure to which the entire system had been subjected. They further pointed out the fallacy of believing that by simple ligation the varicosities could be corrected, and they sought by surgical excision of the offending veins to supplement the benefits attributable to ligation alone. Because of the greater thoroughness and safety of the injection method of treatment, we feel that following high ligation it is better in all save the exceptional case to obliterate the varicosities by injecting sclerosing solutions than by resorting to the old surgical method of excision. It must not be forgotten in the stress that is here laid on high ligation in selected cases that this important operative step must be combined with an effective, thorough and complete subsequent course of treatments by injection if satisfactory results are to be secured.

With the advent of enthusiasm for the treatment of varicose veins by injection a lamentable disregard for underlying considerations soon became apparent, and although the chief sponsors for the use of sclerosing solutions recommended making injections into the main trunk as high in the thigh as it could be made out, many less experienced workers were hesitant in making injections above the knee, and still

5. Mayo, C. J.: Treatment of Varicose Veins, Surg., Gynec. & Obst. **2**:385, 1906.

6. Miller, R. T., Jr.: The Results of Operative Treatment of Varicose Veins of the Leg by the Methods of Trendelenburg and Schede, Bull. Johns Hopkins Hosp. **17**:289, 1906.

7. Homans, John: The Operative Treatment of Varicose Veins and Ulcers, Based on a Classification of These Lesions, Surg., Gynec. & Obst. **22**:143, 1916.

others employed ineffective measures to determine the presence of the main trunk in the thigh. Still more important was the question of the permanence of the artificially produced occluding thrombus in the upper portion of the internal saphenous vein. It seems reasonable to suppose that the tendency to recanalization is greater in the all-important thrombosed upper portion of this vein, where the region is still subject to a certain degree of back pressure, than in the smaller thrombosed branches of the lower part of the leg, where the factor of back pressure had been eliminated. From a practical point of view, our microscopic studies of thrombosed veins and those by de Takáts and Quint,[8] McPheeters and Lufkin[9] and Ochsner and Garside[10] show that recanalization occurs, and the clinical results obtained in the clinic for peripheral vascular conditions of the Massachusetts General Hospital[1] and by Howard and his associates[11] have disappointingly reminded us of the efficacy of nature in reestablishing a lumen in an apparently successfully obliterated vein.

On the basis of the statistical study of our end-results with three hundred and fourteen patients treated by the injection method alone,[1] I believe that 29.3 per cent represents the minimum number of cases in which high ligation is necessary. The proportion of the total number of cases showing marked varicosities is higher and the need for ligation greater in a clinic such as ours than it is among patients who come to a doctor's office for private treatment. The feeling of all of us connected with this work at the Massachusetts General Hospital since the aforementioned statistical study was compiled has been increasingly in favor of preliminary operation. With more careful examination than we at first employed to determine whether or not the main saphenous trunk above the knee is varicosed, we have come to the belief that undoubtedly more, rather than less, than 30 per cent of our cases present at entry our stipulated indications for primary ligation.

Moszkowicz,[12] de Takáts[13] and others have advocated high ligation of the main internal saphenous vein in cases in which the valves in the

8. de Takáts, G., and Quint, H.: The Injection Treatment of Varicose Veins, Surg., Gynec. & Obst. **50**:545, 1930.

9. McPheeters, H. O., and Lufkin, N. H.: Pathological Studies on Injected Varicose Veins, Surg., Gynec. & Obst. **54**:511, 1932.

10. Ochsner, A., and Garside, E.: The Intravenous Injection of Sclerosing Substances, Ann. Surg. **96**:691, 1932.

11. Howard, N. J.; Jackson, C. R., and Mahon, E. J.: Recurrence of Varicose Veins Following Injection: Study of Pathologic Nature of Recurrence and Critical Survey of Injection Method, Arch. Surg. **22**:352 (March) 1931.

12. Moszkowicz, L.: Behandlung der Krampfadern mit Zuckerinjektionen kombiniert mit Venenligatur, Zentralbl. f. Chir. **54**:1732 (July 9) 1927.

13. (*a*) de Takáts, G.: Ambulatory Ligation of the Saphenous Vein, J. A. M. A. **94**:1194 (April 19) 1930. (*b*) de Takáts, G., and Quillin, L.: Ligation of the Saphenous Vein, Report on Two Hundred Ambulatory Operations, Arch. Surg. **26**:72 (Jan.) 1933.

main trunk are shown to be incompetent, as a preliminary step in carrying out the injection method of treatment. However, in reviewing the literature on this subject one is impressed with two facts which are so startling in the light of our experience at the Massachusetts General Hospital as to make it seem worth while to explain in detail our feelings on these points.

In the first place, the importance of dividing the saphenous vein above its highest branches and at the point where it empties into the femoral vein is mentioned frequently but rarely stressed. We feel with Homans [14] that to relieve back pressure completely and finally the great saphenous vein must be ligated at its entrance into the femoral vein in the groin. If a stump of the saphenous vein is left, which includes the remarkably constant three highest tributaries of this vein, namely, the superficial iliac circumflex, the superficial epigastric and the superficial external pudendal veins (all of which branch off within the first 3 cm. as a rule), the permanent success of the operative procedure is seriously jeopardized. This is true because these branches will in time yield to the added thrust of back pressure on them, which ligation at a level below their junction with the main trunk occasions, and through their collaterals varicosed channels will again be established in the leg. The patient pictured in figure 2 underwent ligation in our clinic before we fully appreciated the importance of ligation at the saphenofemoral junction, and within a year the new varicosities on the front of the thigh, which had been established through their collaterals with the three highest saphenous branches, were apparent and of good size. Furthermore, with high ligation as we carry it out, there is no patent upper stump of saphenous vein left in which thrombosis can occur and inadvertently become dislodged. Thus the danger of emboli, although not eliminated, is, we believe, materially reduced.

In the second place, from reading most of the articles one is left with the impression that ligation of the main trunk of the saphenous vein is a trivial affair. We should be the first to agree if one spoke of isolating the main trunk at a convenient point well below the crease in the groin or at one of the lower points of prominence of the vein, and we do not mean to convey the impression that as we carry out the procedure it is a complicated operation. We do feel, however, that to ligate the vein in the fossa ovalis and thus insure a permanently effective dam against the back pressure on the veins in the lower part of the leg is not the simplest of procedures. It is all-important that the dissection should not traumatize surrounding structures, that adequate surgical preparation is carried out, and that a completely aseptic technic is maintained. Failure to locate the vein accurately gives rise to unnecessary

14. (*a*) Homans, J.: The Operative Treatment of Varicose Veins, Varicose Ulcers and Phlebitis, New England J. Med. **200**:965 (May 9) 1929; (*b*) Homans.[7]

injury to the lymphatics and the opening up of "dead space" in the subcutaneous tissue, while roughness in handling the vein itself may result in hemorrhage of serious proportions from the upper end of the saphenous or the femoral vein.

TECHNIC OF EXAMINATION

We believe that a complete physical examination of every patient on whom an operation is to be performed is so obviously a sound procedure as to need no

Fig. 2.—Showing recurrences ten months after too low a ligation of the main saphenous trunk had been carried out. A second ligation, through an incision at least 2 inches (5 cm.) above the old scar shown in the photograph, was made according to the technic described in the text. At this time it could be demonstrated that the recurrences were due to the patent stump of the internal saphenous vein with its three highest branches, which had persisted because of the improperly executed first operation.

explanatory defense. When ulcers of the lower part of the leg are present, the laboratory studies should include a urinalysis, a Wassermann test of the blood and cultures taken from the ulcerous area. The detailed examination of the lower extremities should be primarily concerned with ascertaining the adequacy of the arterial circulation by invariably palpating for pulsations in the dorsalis pedis and

posterior tibial arteries, by excluding symptomatic orthopedic abnormalities and by employing all measures which would help in evaluating the problem that the varicosities themselves present. These measures include Homans'[15] modification of the Schwartz test, that of percussing the varicose main trunk below the knee and determining whether the impulse is conveyed up the vein to the fingers of the other hand, which are firmly pressed over the fossa ovalis. Often when no main trunk of the internal saphenous vein can be seen or made out by the usual methods of palpation, this procedure will be found to be of the greatest assistance in revealing the presence of a large varicosed main trunk. We have also employed the Schwartz test as originally described by Chevrier,[16] which consists in percussing the vein with the fingers of the upper hand. If an impulse can be seen or felt at the knee, it points directly to incompetence of the valves in the intervening portion of the vein. The Trendelenburg test as outlined earlier should always be carried out, and also the von Perthes modification of the test. The modification is used to determine the status of the deep venous circulation, and in cases in which there is a history of old phlebitis it is the easiest method of ascertaining whether or not the varicosities have taken over the burden of acting as the chief means of return of blood from the leg to compensate for previous impairment of the deep venous return. This modification is carried out by having the patient walk about with the tourniquet applied as previously described. If the varicosities become more prominent, the deep veins have been injured by the old phlebitis, and any treatment of them is contraindicated, whereas, if the reverse is true, ligation may be done. The presence and extent of an acute phlebitis, the degree of edema and the size and location of the ulcerations should be carefully noted. As the only effective method of keeping a record of the case, the findings should be entered on a diagrammatic chart of the legs.

INDICATIONS FOR LIGATION

We believe, except as noted under contraindications cited later, that in all cases of varicosities in which the main trunk of the saphenous vein in the thigh is shown to have incompetent valves primary high ligation should be performed in the thigh before injections are carried out in the lower varicosities. Some patients of advanced age in this group were treated conservatively with bandages or local injections into the chief offending veins because their general life expectancy and relative absence of symptoms did not seem to justify the more extensive procedure. Certain other patients with incompetent valves in the main trunk refused to undergo primary high ligation and received treatment by injection, alone, despite our expressed opinion that the results would almost surely be temporary. If both sides present the stipulated indications for operation, bilateral ligation may be done at the same operation. In fifty-eight cases, or 49.5 per cent of our series of one hundred and seventeen cases, the bilateral procedure was carried out.

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15. Homans, J.: Varicose Veins and Ulcer: Methods of Diagnosis and Treatment, Boston M. & S. J. **187**:258 (Aug.) 1922.

16. Chevrier, L.: De l'examen du reflux veineux dans les varices superficielles, Arch. gén. de chir. **1**:45, 1908.

CONTRAINDICATIONS TO LIGATION

We recognize four definite contraindications to high ligation of the internal saphenous vein:

1. That the varicosities are compensatory, as shown by the aforementioned von Perthes test, is definite evidence that no form of treatment should be instituted.

2. The presence of a superficial or deep acute inflammatory process in the groin is a definite reason for delaying the operation until the process has completely subsided. Sufficient time must have elapsed following its recovery (depending on the nature and extent of the inflammation) to make sure that surgical intervention will not cause a flaring up of the old trouble.

3. The occurrence of hemolytic streptococcus organisms in varicose ulcers makes ligation unwise until the infection has been cleared up. We have had three instances in our series of one hundred and seventy-five ligations in which secondary inflammation of the wound in the groin would seem to have been attributable to the virulent organisms present in the ulcer. We felt in these cases that it was our trauma to the potentially involved lymphatics in the groin that gave rise to this trouble. With the use of dressings saturated with surgical solution of chlorinated soda and rest in bed these organisms can usually be eliminated, as shown by repeated cultures of the ulcer. If at first we fail to rid the area of them, temporary measures are taken in the treatment of the ulcer and veins until the virulent organisms can be shown to have disappeared.

The presence of an acute superficial phlebitis of the lower part of the leg or an extensive inflammatory reaction about an ulceration is not a final deterrent in proceeding with high ligation. In these cases, however, of which we have had three in our series, we have treated the patient conservatively with rest in bed, hot moist applications and the like for a period of from three days to a week before operation. In selected cases of acute superficial phlebitis which does not involve the upper half of the thigh, we believe with Homans [14a] that by high interruption of the main saphenous trunk we lessen the danger of extension of the process into the pelvic veins, shorten the period of convalescence and reduce the risk of pulmonary emboli. However, we have consistently been opposed to making injections into veins that have shared in an acute phlebitic process until at least six months after the inflammation has completely subsided.

4. The treatment of a patient temporarily confined to bed is in our minds not justified, as we feel with de Takáts [13a] that the act of walking following operation is not only a convenience to the patient, but, more important, a safeguard against the formation of untoward thromboses

and the occurrence of emboli. We have been requested frequently at the hospital to carry out high ligations on patients temporarily confined to bed from some other operation or to combine our procedure with other operative measures. We have refused to do this, preferring to wait, for the aforementioned reasons, until the patient is ambulatory.

TECHNIC

There has never been any doubt in our minds as to the advisability of hospitalizing the patients for a period ordinarily including two nights and part of three days. We believe that it is important that the patient enter the hospital the night before operation, as an adequate preparation of the field is indispensable and should be carried out with the same thoroughness as for a laparotomy. The groin is a region subject to the most indifferent hygienic care by many patients, and in obese persons who show an outstanding lack of cleanliness in the region of the groin two days are necessary to prepare the patient properly for operation. Our preoperative preparation includes shaving the pubic hair and its extension into the groin, thoroughly cleansing the skin and applying a spica to hold the enveloping sterile towels in place. Any other form of final dressing invariably slips down and leaves exposed the very area one wants most to have covered. We do not make a practice of marking the location of the vein in the groin at the time of examination on entry of the patient, as we have been unable to find a stain which will not irritate the skin or wash off during the night before preparation. If the operator is not completely familiar with the location of the vein he will be greatly helped by having the patient stand beside the operating table after the sterile drapes are removed and by marking by a scratch on the skin or the application of iodine the exact location of the vein in the groin as brought out by percussing the trunk at the knee.

Ordinarily it is not necessary to order preliminary medication, but if the patient is of a nervous temperament, suitable drugs may be employed, as with any surgical procedure. If the patient is required to stand, as suggested earlier, shortly after receiving a medication of morphine he may feel momentarily a bit dizzy and should have some one beside him at the time.

The skin is prepared with tincture of metaphen, and the site of the operation is draped with sterile goods. If the ligation is to be bilateral, one side should be kept covered with a sterile towel while the other is exposed. Ordinarily the side with the most pronounced varicosities is ligated first. A separate set of instruments should be employed for each groin. The foot of the table is elevated about 10 degrees to promote the emptying of the veins during the ligation. The infiltration of the skin is carried out with 1 per cent procaine hydrochloride to which no epinephrine has been added. The line of wheals starts at a point in the deepest crease of the groin from 2 to 4 cm. below Poupart's ligament, directly over the pulsation of the femoral artery, and extends medially along this crease for a distance of 5 cm. The deeper layers are successively infiltrated, frequent traction being exerted on the plunger of the syringe to insure against injecting the procaine hydrochloride solution directly into the circulation. Starting at the medial border of the femoral artery and running parallel to and just below the crease in the groin, a skin incision from 3 to 5 cm. in length (depending on the amount of fat present) is made down to the superficial fascia, which is a well defined structure between the superficial and deep portions of which the saphenous vein lies, surrounded by a considerable amount of loose areolar tissue and fat (fig. 3, *A*).

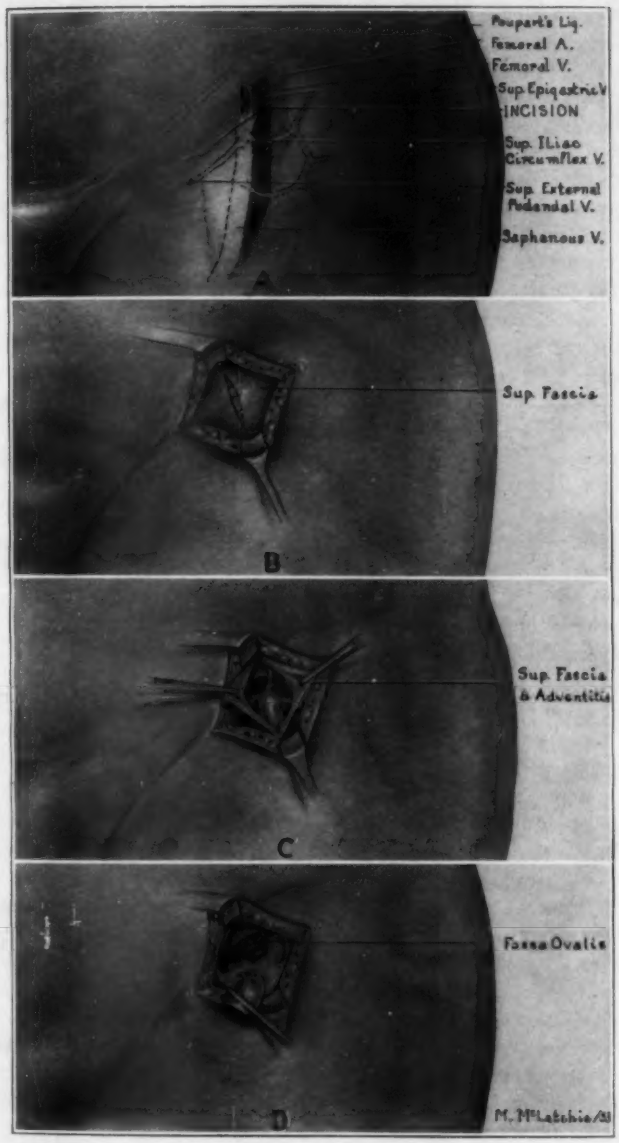

Fig. 3.—Drawings illustrating the operative steps for high ligation of the internal saphenous vein. The details of the procedure are described in the text under the heading "Technic."

The mistake is frequently made in obese persons of seeking the vein in the subcutaneous fat above the layer of superficial fascia before the operator realizes that he has occasioned a certain amount of unnecessary trauma by not proceeding deeply enough with the dissection.

With retraction at the upper and lower margins of the wound, the superficial fascia with its associated underlying areolar tissue is vertically incised, and the saphenous vein found to be directly beneath (fig. 3, *B*). If the operator is uncertain of his landmarks, a transverse incision instead of a vertical incision through this fascia will facilitate the location of the vein. The adventitia, which is made up of a number of layers, is carefully picked up with forceps at the most convenient central portion of the wound and incised in a vertical direction over a distance of 1 cm. The dissection should be carried down to the natural line of cleavage formed by the smooth underlying surface of the vein. When this is reached, the layers comprising the adventitia, with those of the already incised superficial fascia, are grasped on both sides by hemostats, and the incision in the adventitia is carried up and down to give adequate exposure (fig. 3, *C*). This step helps tremendously in the subsequent freeing of the vein and its highest branches. At this stage a curved half-length can be readily passed beneath the vein, which is clamped with two straight hemostats 1 cm. apart. The main trunk is divided midway between the clamps to facilitate the isolation of the upper end and the exposition of its branches. These latter, of which there are always at least the three already mentioned, are separately snapped, divided and directly tied off to keep the field of operation as free as possible from encumbering instruments. The upper end of the internal saphenous vein is exposed as it dips through the fossa ovalis until its point of junction with the femoral vein can be made out. A no. 2 chromic catgut ligature is placed just distal to this point to prevent puckering of the femoral vein, and a second tie, 0.5 cm. distal to the first, is used as an added reenforcement. The upper segment of the vein is again divided just below the second tie in order to remove the portion traumatized by the upper hemostat (fig. 3, *D*).

It has seemed reasonable to us to attempt obliteration by retrograde injection at the time of operation of at least a portion of the saphenous vein in the thigh, as suggested by Moszkowicz.[12] Before the wound is closed, the edges of the end of the vein showing above the hemostat are grasped on both sides; the clamp is removed and the cannula (fig. 4), devised by the author to fit a vein of any size, is tied in position. The leakage of blood through the cannula while one is waiting for the syringe of the sclerosing solution may be prevented by angulating the vein forward over the lower edge of the superficial fascia. We have used from 10 to 20 cc. of a solution of 30 per cent invert sugar and 10 per cent sodium chloride with each injection, depending on the size of the vein. By elevating the leg, pressing over the trunk in the midthigh and aspirating the blood from the vein, we have attempted at least partially to empty the vein before injections are carried out. Following the injection, the vein is tied off below the cannula, and with traction on the plunger of the syringe to prevent the escape of any of the solution into the tissues, the vein is again divided just below the cannula and above this last placed tie. The wound is flushed out with salt solution; the edges of the superficial fascia are brought together with one or two plain catgut sutures to obliterate any "dead space" and the skin is closed with interrupted silk stitches. A small square of gauze is held in place by a piece of adhesive tape in which an air

vent has been cut to serve as a dressing, and Bender bandages are applied to the lower parts of the legs.

After-Care.—We believe that the patient should be forced to a certain extent to be ambulatory following the operation in order that the muscles of the leg by their pumping action in walking may help to dissipate any sluggishness in the venous return and so reduce the likelihood of untoward thromboses and emboli. To that end we have the patients walk a few steps from the operating room truck to their beds following ligation and then accord them lavatory privileges so that at intervals they may be active. It is a mistake to feel that there is no significant difference between having the patients ambulatory after operation and merely having them out of bed in a chair. The former is to be encouraged as of definite benefit to them, whereas the latter is to be condemned, since, with the passive dependence of the lower extremities, venous stagnation is actually increased. When the patient has returned from the operating room, the foot of the bed is

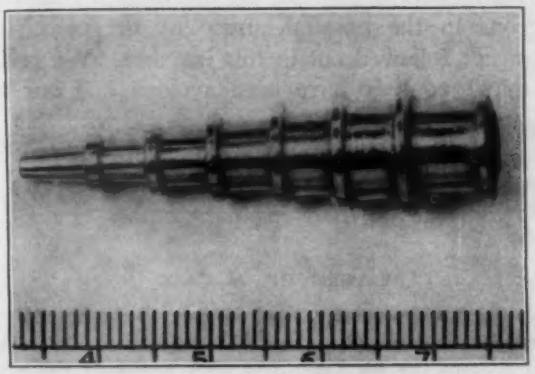

Fig. 4.—The cannula used for the retrograde injection of a sclerosing solution into the distal end of the vein at the time of operation.

elevated on a chair with the same idea in mind of aiding venous return in the legs. Following ligation, the wounds in the groin give little discomfort, but it is not uncommon for the area in the thigh into which injections have been made to show the somewhat uncomfortable reaction of tenderness along the course of the vein that is often associated with the use of sclerosing solutions. Barring complications, the patient, still wearing the Bender bandages below the knee, leaves the hospital the day following the operation, but he is instructed to avoid strenuous exertion during the following week. The stitches are removed on the fifth or sixth day, and all dressings are abandoned a day or so later.

The course of treatments by injection is started as soon as the wound is healed and may be carried out according to the operator's method of choice so long as the final result is a firm thrombosis of every varix that can be detected by inspection or palpation. Fewer visits (usually from three to five) are required in cases of injections following the preliminary operative step than in cases in which there is no preliminary operation. This is due to the fact that by high ligation and retrograde injection not only is the upper portion of the saphenous system thrombosed, but the remaining varicosities (relieved of the back pressure formerly

exerted on them) are less distended and less prone to show "excessive reactions" and respond over a greater extent to each injection than in the cases in which operation has not been performed.

COMPLICATIONS

The procedure may be followed by certain complications which contribute largely to our feeling that the operation is definitely not without its risks. The most serious untoward event is postoperative pulmonary emboli.

In the series of one hundred and seventeen cases we have not seen this complication, but since these figures were compiled we have had one fatality from a postoperative pulmonary embolus following ligation of the veins. The details of this case are significant, owing to the fact that through faulty liaison between the members of our clinic and the resident surgeons in the hospital, many of the principles we have advocated were not followed out in this instance. We believe that the complication might possibly have been avoided had our technic been carefully followed. Feeling that the experience with this patient substantiates the importance of closely adhering to our stipulated rules for operation, the salient features of the history, with certain explanatory comments, are given in the following paragraphs.

REPORT OF A CASE

An extremely obese white woman, aged 54, entered the hospital on the recommendation of the outpatient surgeon in our clinic because of bilateral varicose veins which had been present for ten years and were becoming progressively worse. They had been complicated for three months by an ulceration above the left internal malleolus. The varicosities were large; they involved only the internal saphenous system and showed incompetence of the valves in the main trunk in the thigh but essentially no impairment of the valves in the perforating branches of the lower part of the leg. There was pigmentation of the skin above the left internal malleolus with a crusted lesion 1 cm. in diameter in the same region. The ankles showed a slight amount of pitting edema which the patient had noticed off and on for several years. The peripheral arterial circulation was good, but the general circulatory condition showed a considerable degree of arteriosclerosis with a hypertension of 198 systolic and 110 diastolic and slight cardiac enlargement. The most striking feature of the marked obesity was the panniculus of fat which hung down and obscured the creases in the groins. The patient received a single preparation of the field of operation on entry, and the following day had the internal saphenous veins ligated in the groin and interrupted a second time at the level of the knee. The operator's note stated that because of the great amount of subcutaneous fat he could not demonstrate the saphenofemoral junctions. Retrograde injection into the vein on the left was carried out with 20 cc. of the sugar and salt preparation; Bender bandages were applied to the lower parts of the legs, and the foot of the bed was elevated when the patient returned to the ward. Twenty-four hours after the operation the temperature was 101 F., and there was slight tenderness at the lower incisions. On the following day the patient was allowed to sit

in a wheel-chair, and hot, moist applications were applied to the areas of induration. Two days later the wounds were opened; cultures showed a pure growth of hemolytic streptococci. The wounds improved, and the temperature returned to normal. On the eleventh postoperative day the patient suddenly presented the typical picture of a massive pulmonary embolus and died. Permission for an autopsy was refused by her family.

In retrospect, we feel that at least two days were needed to prepare the patient properly for the operation, that cultures from the crusted ulceration should have been taken and reported on before ligation was carried out, and that the patient should not have been allowed to sit passively in a wheel-chair during convalescence. The ligation should have been made at the saphenofemoral junction; the second interruption of the main saphenous trunk at the level of the knee should not have been carried out.

We have not mentioned the procedure of interrupting the main saphenous trunk a second time at the level of the knee because we feel from our experience in adopting this added operative step in 50 per cent of the ligations in this series that both the theoretical and the clinical advantages are not justified by the added risk. The wounds at the knee, as in the case cited, have shown a marked tendency to heal poorly as contrasted with those in the groin, and we no longer practice or advocate a second interruption of the main saphenous vein below the ligation in the groin.

In seven, or 5.9 per cent, of our cases a varying degree of secondary inflammation has been evident about the wound, necessitating hospitalization beyond the usual period. We feel that the reasons for this complication can be traced to faulty operative technic, contamination of the wound with the sclerosing solution or failure to observe our stipulated set of rules of contraindications.

Hemorrhage at the time of operation or later has not been a complication in any of our cases.

RESULTS

Our end-results in this series of cases will be determined within the next few months, so that at present we have only a strong conviction based on our untabulated subsequent observation of these patients and the findings of others [17] that the underlying principles we have advocated here are sound. We believe, in cases in which the valves in the main trunk above the knee can be shown to be incompetent, that the results obtained by the combination of high ligation and subsequent injections will show a definite improvement over those obtained with injections alone or with the older forms of radical surgery.

17. Moszkowicz.[12] de Takáts.[18b]

It is outside the scope of this paper to elaborate on the subject of the treatment of ulcers, varicosities of the short saphenous vein or the problems presented by incompetent valves in the communicating branches in the lower part of the leg. These must be dealt with when present, and when found, as they usually are, in conjunction with a varicosed internal saphenous vein in the thigh, we believe that treatment must include high ligation in the groin.

SUMMARY AND CONCLUSIONS

1. In cases of varicosities of the internal saphenous system in which it can be shown that the valves in the main trunk are incompetent, ligation of the vein in the groin is an indispensable adjunct to any form of treatment, since it affords the only permanent means of relieving the varicosities of the lower part of the leg from the back pressure exerted on them from above.

2. To be effective the vein should be tied off at the saphenofemoral junction, above its three highest tributaries, which would otherwise open up collateral venous channels around the point of ligation.

3. At least 30 per cent of all of the cases seen in the clinic of the Massachusettts General Hospital present at entry indications for preliminary high ligation.

4. If virulent organisms can be demonstrated in a complicating ulcer, or if there is any inflammatory process in the groin, high ligation must be postponed until these conditions have completely subsided under conservative treatment.

5. Patients on whom preliminary high ligation has been carried out should remain ambulatory following operation.

6. The procedure requires a short period of hospitalization to insure the advantages of proper operating facilities and adequate preoperative preparation of the field of operation.

7. Retrograde injection of a sclerosing solution into the distal segment of the vein at the time of operation is of advantage in supplementing the benefits of ligation alone.

8. A thorough course of injections which, because of the preliminary ligation, will entail fewer visits by the patient must be instituted following operation if the end-results in the treatment of the veins is to be satisfactory.

9. Adherence to the technic and principles here stipulated will materially reduce the incidence of complications.

10. From our experience in one hundred and seventy-five ligations we believe that the combination of high ligation and subsequent injections in cases in which the valves of the main trunk are incompetent offers a better chance of permanent cure than any other method of treatment, including the old extensive surgical procedures.

264 Beacon Street.

AVERTIN IN PREANESTHETIC MEDICATION

A SURVEY OF 1,831 SURGICAL ANESTHESIAS

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During a survey of the use of avertin in the general surgical service since 1930, certain points were noted which when correlated with known reactions to avertin were deemed of sufficient interest to merit publication. The number of cases in which avertin was used and their general distribution as to types of surgical procedures are considered sufficient to permit a comparison of the influence of age and sex on the response to a range of doses, as well as of the adaptability of this substance for different types of surgical procedures and for use with different supplementary anesthetics. This report also permits a direct comparison of the relative premedication values of two entirely different types of hypnotics, i. e., avertin (tribromethyl alcohol) and pentobarbital sodium (sodium ethyl [1-methyl-butyl] malonyl urea) used for similar purposes in the same surgical service. The report on pentobarbital sodium will appear separately.

The age range of the patients, the nature and frequency of the surgical procedures, the doses of avertin and the anesthetic supplements used are shown in table 1.

PROCEDURES

During the evening preceding the day of operation apprehensive patients received a sedative (usually of the barbital type) in order to assure a restful preoperative night. However, 80 per cent of the group required no medication. In addition, the colon was cleansed by a warm enema. On the following morning from thirty to sixty minutes before the scheduled operation, morphine (⅙ grain [11 mg.]) and atropine (1/150 grain [0.5 mg.]) or fractional doses of this combination as gaged by age were administered hypodermically to 88 per cent of the patients. The remainder (including the group who were to undergo operations on the brain) received either atropine alone or no supplementary premedication. Ten minutes after the injection of morphine and atropine, avertin—the dose gaged by the age, weight and general condition of the patient—was administered rectally over a five minute period as a freshly prepared, warm, 2.5 per cent aqueous solution of avertin fluid. The patients were asleep within from two to ten

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minutes after the rectal instillation had been completed and could be transported to the operating room. The administration of the supplementary anesthetic was begun from fifteen to thirty minutes after the injection of avertin.

The routine observations included pulse and respiratory rates and systolic and diastolic blood pressures before premedication and after premedication, i. e., just before the administration of the supplementary anesthetic, during the course of the operation and postoperatively on return to bed. The urine was examined for albumin, casts and cells on admittance and for several days postoperatively. Postoperative nausea, vomiting, restlessness and pulmonary complications were likewise observed. In a small selected group of cases respiratory minute volumes were recorded by means of a Bohr gas meter before and after the administration of both the narcotic and a range of doses of the hypnotic. This was done to determine the degree of respiratory depression produced by this sequence of premedication.

TABLE 1.—*Distribution of 1,831 Patients as to Age, Type of Operation, Dose of Avertin and Anesthetic Supplement*

Age Groups		General Surgical Groups		Anesthetic Supplement Groups		Avertin Fluid Groups	
Years	Per Cent of Total No. of Patients	Operative Region	No. of Patients	Nature of Supplement	Per Cent of Total No. of Patients	Dose, Mg. per Kg.	Per Cent of Total No. of Patients
4 or less	5.86	Head	78	None	5.51	35 to 50	3.60
7 to 10	6.80	Face	38	Local	4.90	60	8.37
11 to 20	14.84	Nose	78	Ether	7.20	70	9.57
21 to 45	54.06	Neck	186	Nitrous oxide and oxygen	27.90	80	32.82
46 to 65	16.55	Chest	7	Nitrous oxide, oxygen and ether	54.49	90	25.64
		Breast	56			100	20.00
		Back	26				
		Abdomen	310				
		Pelvis	631				
		Extremities	504				
		Transfusion	5				
		Dressing	11				

Initially the observations were tabulated according to the doses of avertin and subdivided according to the types of surgical procedures, irrespective of the supplementary anesthetics used. The data thus obtained were analyzed, but a regrouping of the original observations according to the types of supplementary anesthetics and subdividing according to the doses of avertin yielded simpler and equally satisfactory data and will therefore be used in this presentation.

Four surgical groups, including patients subjected to operations on the thyroid gland, gallbladder and brain and gynecological operations, differed so significantly in their reactions to anesthesia and during the postoperative period as indicated by the first analysis that these four groups have been studied separately. The reactions of the remainder of the 585 patients on whom detailed studies were made were so similar that the observations are massed and the data presented as medians in a general tabulation including an age range of from 19 to 60 years (chart 1) and smaller subdivisions (chart 2) including young (from

1½ to 18 years), intermediate (from 19 to 39 years) and older patients (40 or more years of age).

The anesthetic supplement used, except in the special surgical groups, was adapted to the patient according to the judgment of the surgeon, but no routine or fixed procedures were established. A nitrous oxide, oxygen and ether supplement was used most frequently (in 55 per cent of the entire series) and represents the anesthetic of choice.

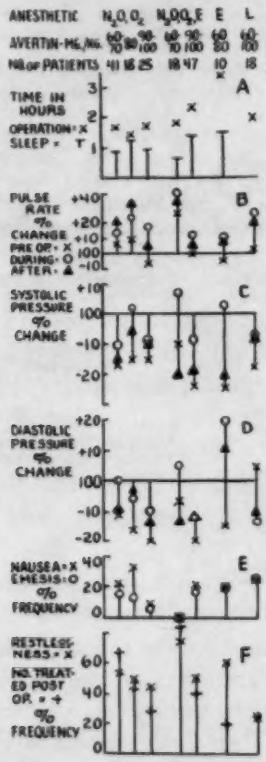

Chart 1.—The data massed according to the anesthetic supplements that were used.

In all the charts the symbols N_2O,O_2 N_2O,O_2,F *E* and *L* at the top represent the anesthetic supplements nitrous oxide and oxygen, nitrous oxide, oxygen and ether, ether and a local anesthetic; the numbers in the second line, the milligrams of avertin administered per kilogram of body weight, and those in the third line, the number of patients whose anesthetic records are tabulated below.

OBSERVATIONS BEFORE OPERATION

Condition of the Patient on Arrival at the Operating Room.—Ninety-two per cent of the patients were asleep on arrival, usually well relaxed and satisfactorily analgesic. Occasionally with doses of 70 mg. or less of avertin per kilogram of body weight patients moved slightly on

arrival, but this was much more frequent after doses of from 50 to 60 mg. In general, the reactions on being moved were unimportant, but were observed in the presence of painful stimuli, irrespective of the dose administered.

Respiration.—The respiratory rate was either unchanged or increased slightly by premedication. As a rule, however, oscillations of one or two respirations on either side of the normal rate occurred.

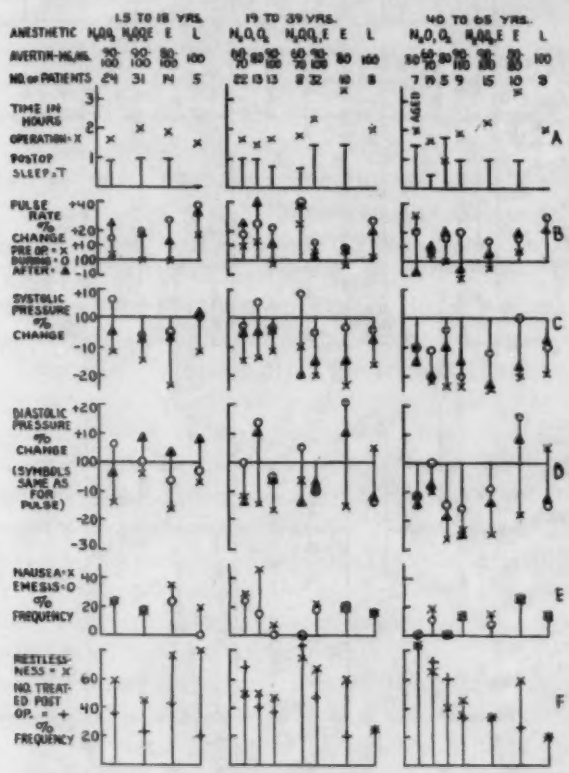

Chart 2.—The data massed according to the ages of the patients.

Occasionally following medication with heavy doses of the hypnotic or even with moderate doses in sensitive persons a significant respiratory depression was observed. Under such conditions the rate was increased and the volume decreased. Depression of the minute volume occurred with all doses. Morphine in the dose used (⅙ grain) depressed the minute volume approximately 5 per cent. The net depression due to avertin in doses of from 80 to 100 mg. per kilogram of body weight varied from 30 to 50 per cent. One patient medicated with morphine (⅙ grain) and 90 mg. of avertin per kilogram showed a decrease of

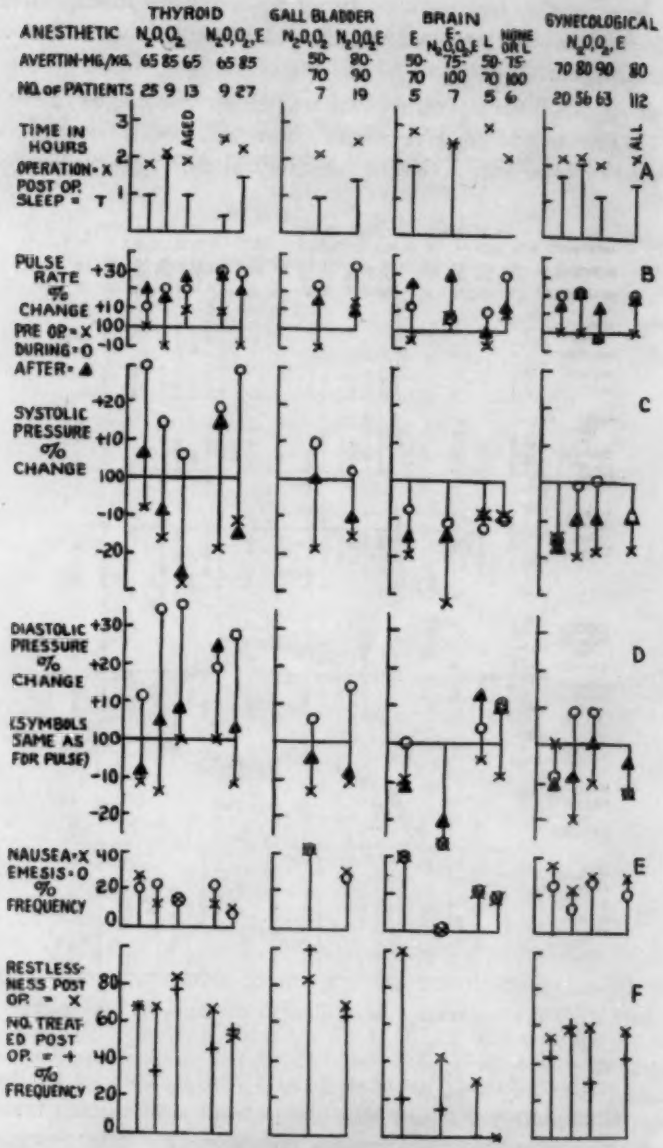

Chart 3.—The data on four special surgical groups, massed according to the types of surgical procedures involved.

70 per cent in the minute volume. The degree of depression was grossly proportional to the dose administered. With a dose of 70 mg., the minute volume diminished from 22 to 29 per cent.

Pulse Rate.—The preoperative pulse (indicated by the symbol *X* in charts 1, 2 and 3, part *B*) was irregular and was unchanged, increased from 5 to 25 per cent or decreased from 2 to 10 per cent. The median change with doses of 70 mg. per kilogram or less was a rise of from 3 to 12 per cent above the level on admittance. With larger doses the pulse was either unchanged or depressed slightly (from 3 to 6 per cent). Exceptionally the pulse varied from 12 per cent below to 18 per cent above the normal values even with doses of 100 mg. In patients less than 18 or more than 60 years of age the pulse rate was the least stable and reacted the most variably. Differences due to sex (with similar ages and premedication) appeared unimportant.

Blood Pressure.—The systolic blood pressure following premedication with avertin varied markedly even with the same dose, particularly as to the time at which the change from normal occurred. Occasionally the initial fall was not observed until after the administration of the general anesthetic had been begun, owing probably to individual variability as to the rate of absorption from the rectum. The median picture was one of depression, which varied in degree from 10 to 40 per cent (the latter rarely), with an average fall of 18 per cent. The systolic fall was proportional to the dose of avertin, as indicated by the extremes in the entire group, but differences in the degree of fall in groups of equal age may be insignificant with a dose ranging from 60 to 100 mg. per kilogram of body weight (chart 1). Patients in the age range of from 40 to 65 years, particularly the aged, showed the greatest degree of depression. Women showed a greater systolic fall than did men under similar conditions of age and medication.

The diastolic pressure showed a much better correlation with the dose of the hypnotic administered than did the systolic pressure. Depression was the rule, the degree of which was somewhat less than the systolic change with small to medium doses (50 to 70 mg. per kilogram), but closely approximated the systolic change with larger doses. The fall increased with the dose and, irrespective of the dose, increased with age (chart 2). The diastolic pressure was depressed to a greater degree in females than in males of the same age under similar medication.

Nature of the Anesthesia (Charts 1 and 2).—The induction or transition period between the premedication state and surgical anesthesia was short. From 80 to 85 per cent of the anesthesias were considered good and the remainder fair or poor. Poor anesthesias were more frequent with small doses of avertin (from 50 to 70 mg.) than with large ones (from 85 to 100 mg.) and, so far as the supplements were con-

cerned, were more frequent with ether than with nitrous oxide and oxygen or with nitrous oxide, oxygen and ether. No poor anesthesias were recorded in the group receiving local anesthetics. One disagreeable feature observed in the use of local anesthesia was that patients reacted by movements, and occasionally complained even when medicated with from 90 to 100 mg. of avertin per kilogram of body weight. The anesthesia was somewhat better and more regular with young patients (under 18 years) than with older subjects. Smaller quantities of the supplementary anesthetic were required after large doses than after small doses of avertin. Heavily premedicated patients were simply nearer the stage of basal narcosis. Anesthesia was somewhat less satisfactory in female than in male patients, independent of age or the dose of avertin administered.

OBSERVATIONS DURING AND FOLLOWING OPERATIONS

Pulse Rate.—During operation the pulse rate increased from 10 to 40 per cent above normal, as indicated by the symbol *O* in the charts (part *B*). The increase was grossly proportional to the dose of the hypnotic administered under constant conditions as to age and supplementary anesthetic. Exceptionally, quite wide variations occurred, but generally with minimal doses of avertin. The nature of the supplementary anesthetic administered bore some relation to the changes in the pulse rate; i. e., with the exception of the age group from 1½ to 17 years, the increase was least with ether anesthesia and maximal with local anesthesia. The changes were greatest in young patients and decreased progressively with increasing age. Smaller changes occurred in females than in males.

Postoperatively the pulse rate varied from the level established during the operation with both the dose of the hypnotic and the nature of the anesthetic supplement; i. e., the pulse tended to increase with small doses of avertin (50 to 75 mg.) and to fall after maximal doses (above 85 mg.). Ether, nitrous oxide, oxygen and ether or local supplements in the main either inhibited a further rise or depressed the postoperative pulse rate.

Blood Pressure.—During the operation the systolic pressure increased as a rule and partially or completely compensated for the fall which occurred preoperatively, so that with the exception of those receiving small doses of avertin and the aged ones the values were from 3 to 10 per cent below (exceptionally above) the normal values. The degree of recovery was greatest with young and least with aged patients. The depression of the vasomotor center was proportional to the dose of avertin administered. Postoperatively the median systolic pressures were from 4 to 25 per cent below the original normal values; normal levels were exceptional.

Diastolic pressures both during operation and postoperatively were extremely variable. The significance of the data is questionable, but the systolic and diastolic oscillations were grossly parallel.

Respiration.—The respiratory rate increased from 30 to 60 per cent during the course of the anesthesia. The changes were greatest with nitrous oxide and oxygen and least with an ether supplement. The volume became distinctly more shallow than normal and compensated partly for the change in rate. The respiratory depression was apparent, and although it was possible to maintain surgical anesthesia in the absence of cyanosis in the great majority of patients, the margin of safety was narrow and the responsiveness to carbon dioxide or rebreathing was distinctly diminished during the first thirty to forty-five minutes of anesthesia. These difficulties diminished as the operation progressed owing to the fact that the depressive effects of avertin were wearing off. Postoperatively the respiratory rates varied on either side of normal, but more frequently remained slightly above normal for from one to two hours. The minute volumes remained below normal for variable periods (duration of postoperative sleep), and occasionally cyanosis developed.

Restlessness.—Movements during the period of operation rarely occurred, but were noted occasionally even after medication with maximal doses of the hypnotic (100 mg. per kilogram) and morphine (⅙ grain) supplemented with nitrous oxide and oxygen. Such reactions were most frequent after small doses of avertin, but were not unusual in the presence of local anesthesia, irrespective of the dose of avertin administered.

Postoperative restlessness was observed more frequently than would be expected from previous reports. The frequency of occurrence bore an inverse relation to the dose of avertin. The frequency was lower with local than with other supplements. At least part of the postoperative reactions were due to the general anesthetic. Ether exaggerated the reaction to avertin to the greatest degree and nitrous oxide and oxygen least. The frequency of occurrence, as well as the percentage of the entire group of patients medicated postoperatively either for pain, restlessness or both, is illustrated in the charts. The postanesthetic movements noted following medication with avertin, although as frequent as with pentobarbital sodium, were distinctly less troublesome, and the patients required less nursing attention.

Postoperative Sleep.—The interval between the conclusion of the operative procedures and return of consciousness bore little if any relation to the dose of avertin administered. In general, the duration was greatest with ether, less with nitrous oxide, oxygen and ether and least with ethylene and oxygen. No postoperative sleep was observed

in the group receiving local anesthesia. It appears, therefore, that the duration of the operation and the degree of depression due to the anesthetic per se are of greater significance in governing the time of postoperative depression than the medication with avertin. The depressive effects of avertin have probably largely worn off by the time the surgical procedures are completed. Patients within the age range of from 1 to 18 years were medicated with from 90 to 100 mg. (median, 100 mg.) of avertin per kilogram of body weight. On the basis of the total time of unconsciousness (operation and postoperative sleep) the immature patients appeared most tolerant to maximal doses of avertin. However, both aged and young patients were more deeply narcotized than were patients of intermediate ages. The quantities of the supplementary anesthetics required in the extremes of age were less than in the intermediate ages (the hypnotic dose and anesthetic being constant), and the operative procedures were of less severity and of shorter duration in the young age group. Young patients are probably not more tolerant to avertin than are other age groups; on the contrary, as suggested by experimental studies of toxicity (Barlow), both young and aged patients are more sensitive to avertin, as evidenced by the greater percentage of patients in these two age groups who required no supplementary anesthetic. However, the lower frequency of organic lesions and the greater recuperative capacity of young subjects as compared with other age groups may be of significance during the postoperative as well as later periods.

Nausea and Vomiting.—Nausea was observed postoperatively in approximately 20 per cent of the general surgical patients. No clearcut relation between the frequency of its occurrence and the dose of avertin is apparent from the data. There are, however, indications that nausea occurred more frequently with small than with large doses and was somewhat greater in the presence of ether than with other supplements. Following nitrous oxide and oxygen anesthesia, emesis occurred less frequently (age group below 19 years excepted) than nausea. The majority of patients nauseated following anesthesia with supplements other than nitrous oxide and oxygen also vomited. Nausea and emesis were more frequent in females than in males in the age extremes, irrespective of the dose of avertin or the nature of the supplementary anesthetic. No difference related to sex was apparent in the group from 18 to 39 years of age. The divergence of this single group may be accidental.

Amnesia.—Eighty-five per cent of patients medicated with avertin had complete amnesia for from two to six hours after operation. The remaining 15 per cent had amnesia of more than six hours' duration. The period of amnesia was directly proportional to the dose of avertin.

In rare instances, irrespective of age, patients who received small doses of avertin supplemented with local anesthetics talked rationally during the course of the operation, and one patient subjected to a laminectomy remembered the incision being made.

Urinary Findings.—The first specimens of urine taken postoperatively showed traces of albumin in a certain percentage of all types of cases. The frequency was lowest in the orthopedic group, which included immature patients predominantly, and highest in the gallbladder and thyroid groups. In other surgical groups the frequency was intermediate. The albuminuria in patients free from albumin preoperatively ranged from a faint trace to 4 +. Albuminuria was present in 39 per cent of the entire group studied in detail. Relatively few of the specimens from females were obtained by catheterization; however, 28.7 per cent of the specimens from males likewise showed albumin, so that the incidence remained high. The specimens taken forty-eight hours after operation were albumin-free as a rule, but occasionally traces persisted for five or more days. The frequency of albuminuria bore little relation to the nature of the anesthetic supplement used, and the condition was observed with approximately the same frequency after medication with from 50 to 60 mg. as with from 80 to 90 mg. of avertin. The frequency bore a definite relation to the type of surgical case: greatest in the gallbladder group, next most frequent in the thyroid group and slightly less frequent in the group operated on for hernia and that treated by plastic surgery. The frequency was significantly higher in patients more than 35 years of age.

Hyaline and occasionally granular casts were observed postoperatively in 7 per cent of the total number of specimens studied. More than 90 per cent of the specimens showing casts postoperatively had not shown casts preoperatively. The specimens taken from forty-eight to seventy-two hours after operation were as a rule free from casts, but occasionally these persisted for several days. Specimens obtained from a 3 year old patient, although normal preoperatively, contained both albumin and casts for from seven to nine days postoperatively. Casts were usually absent from the urine of orthopedic patients and those who had undergone operations on the brain or the breast, but the frequency bore little relation otherwise to the type of surgical case. The frequency was no greater with large than with small doses of avertin, but this lack of correlation was only apparent in that older patients were medicated with minimal doses of the hypnotic .

Red and white blood cells were occasionally reported in the urine postoperatively, but in 2 of 3 cases the preoperative conditions remained unchanged. So far as cells were concerned the specimens were considered as containing none.

Traces of sugar were observed postoperatively in a small proportion of specimens. In one case values of 10 mg. per hundred cubic centimeters were observed, and the glycosuria persisted for more than a week. With few exceptions, however, glycosuria following this anesthetic sequence was no more frequent or greater in degree than in the absence of avertin.

OBSERVATIONS ON SPECIAL SURGICAL GROUPS

Nature of the Anesthesia.—Thyroid: The optimal anesthetic sequence for operations on the thyroid appeared to be morphine (⅙ grain), atropine (1/150 grain) and avertin (from 80 to 90 mg. per kilogram), supplemented with nitrous oxide and oxygen. All anesthesias obtained with this sequence were good. With smaller doses of avertin (from 60 to 70 mg.) anesthesias were distinctly less satisfactory, irrespective of whether nitrous oxide and oxygen or nitrous oxide, oxygen and ether were administered, but aged patients responded somewhat better than younger patients.

Gallbladder: In the group which was operated on for disease of the gallbladder the anesthesia and the relaxation obtained following medication with morphine and avertin (from 80 to 90 mg.) and the administration of nitrous oxide oxygen and ether were distinctly better than with lower doses of the hypnotic. Aged patients received smaller doses of avertin (from 50 to 70 mg.), and nitrous oxide and oxygen as a supplement. A greater percentage of fair anesthesias was obtained with this sequence than with that including nitrous oxide, oxygen and ether.

Brain: The optimal anesthetic sequence in this group, as judged by the observations made, was avertin in doses of from 50 to 70 mg. per kilogram, supplemented with local anesthesia. The frequency of movements during the course of the anesthesia was considerable, however. Ether, although somewhat less satisfactory owing to the greater frequency with which side actions occurred, nevertheless was the anesthetic of choice, in that relaxation was maximal and anesthesia complete. Avertin in doses of from 75 to 100 mg. per kilogram produced a narcosis of such degree that in 2 of the 13 patients no supplementary anesthetic was required. With such maximal doses of the hypnotic, local anesthesia was least and nitrous oxide, oxygen and ether most satisfactory.

Gynecological: Ninety-seven per cent of the anesthesias following medication with morphine (⅙ grain), atropine (1/150 grain) and 80 mg. of avertin per kilogram were satisfactory in the presence of a nitrous oxide, oxygen and ether supplement. Poor anesthesias were

exceptional (3 per cent). A greater percentage of "fair" anesthesias was obtained after medication with smaller doses, and although the anesthesia obtained in the presence of larger doses of the hypnotic was generally excellent, a greater percentage of poor anesthesias was noted than with medium doses.

Pulse Rate.—The median change in pulse rate following premedication was unimportant. No change was noted in the gynecological group, irrespective of the dose of the hypnotic. With the remaining groups the data suggest that directional changes are inverse to the change in systolic pressure. The correlation is imperfect, however; i. e., the variability is within a range of plus or minus 10 per cent, and may be insignificant.

During the operation the pulse rates of the thyroid group increased from 10 to 25 per cent above the values on admittance (100 per cent). The degree of change was proportional to the hypnotic dose. Comparable changes occurred with other groups. The altered pulse rate was probably compensatory for the altered blood pressure, but the correlation with either systolic or diastolic pressure was imperfect. Postoperatively the pulse rate remained somewhat above normal.

Blood Pressure.—In the thyroid group the depression of the systolic pressure following medication was proportional to the dose of the hypnotic administered; i. e., a median decrease of 7.5 per cent occurred with doses of from 60 to 70 mg. per kilogram and a fall of 16 per cent with from 80 to 90 mg. The systolic change was significantly greater in patients more than 50 years of age than in younger subjects, even with minimal doses of avertin. The diastolic pressures grossly paralleled the systolic levels, but were more variable. The aged group proved the exception in that, although the systolic pressure was reduced maximally, the diastolic pressure remained unchanged; i. e., it actually increased in relation to the systolic level. During the course of operation the systolic pressure increased above normal. The degree of rise from the preoperative level was greatest in the presence of small doses of the hypnotic. Postoperatively the systolic pressure decreased from the anesthetic level; i. e., with minimal doses of the hypnotic the pressures noted with middle-aged subjects remained slightly above normal, but fell below normal with maximal doses. The fall noted in aged patients was distinctly greater even with minimal doses of the hypnotic than the fall observed in younger subjects. The diastolic pressures remained within a normal range postoperatively.

In the gallbladder, brain and gynecological groups the median preoperative blood pressures differed insignificantly from those discussed for the thyroid group, but the rise during anesthesia as well as the postoperative fall was of smaller magnitude in these groups than in the thyroid group.

The rise in blood pressure during anesthesia was least with ether and greatest with nitrous oxide and oxygen. The supposedly transient fall in blood pressure as indicated by the preoperative level is probably of greater duration than is generally appreciated. The depression of the circulatory system by avertin is maximal during the thirty to forty minutes following rectal instillation, but persists to a modified degree for at least from ninety to one hundred and twenty minutes longer. The rise from the medication level which occurs on the administration of the general anesthetic is partly due to anoxemia per se, in that the rise is maximal with nitrous oxide and oxygen and minimal with ether. Surgical manipulation is likewise contributory, as indicated by the changes noted in the group receiving a local anesthetic (with cerebral involvement), as well as in the absence of any supplementary anesthetic. The postoperative fall is due partly to removal of the stimulant effects of the anesthetic and to surgical insult, but quite probably the persistent depressant effects of avertin are also contributory.

Period of Postoperative Sleep.—The duration of the postoperative unconsciousness was slightly longer in the thyroid, gallbladder and gynecological groups than in the massed series of surgical cases, irrespective of the dose of avertin administered or the nature of the anesthetic supplement used. Of the special surgical groups, those in the thyroid group recovered earliest, then those in the gallbladder and gynecological groups. In the brain group, no postoperative sleep was observed. The absence of significant postoperative depression in patients subjected to avertin and local anesthesia suggests that any effects of avertin persisting on conclusion of surgical procedures were insufficient to produce even moderate hypnosis, and that variations in the time required for the return of consciousness are explainable partly by the hangover effects of the supplementary anesthetic but more probably by the depressant effects of the surgical procedures. This explanation would seem to be substantiated by the fact that 2 patients who received large doses of avertin but no supplementary anesthetic, and who were subjected to operations on the brain slept one and seven and one-half hours, respectively.

Restlessness.—More than half the patients in the gallbladder, thyroid and gynecological groups were restless postoperatively. The frequency was in the order named. Patients in the thyroid group receiving medication with small or large doses of avertin were equally restless whether nitrous oxide and oxygen or nitrous oxide, oxygen and ether were used for supplementary anesthesia. Aged patients were more restless than younger subjects. In the gallbladder group patients were slightly more restless after small than after large doses of avertin, but those receiving large doses were given nitrous oxide, ogygen and ether while those receiving small doses (including a greater percentage of aged patients) received nitrous oxide and oxygen. The frequency with which restless-

ness occurred in the gynecological group was independent of the dose of avertin. The occurrence of restlessness in the brain group may have some relation to the dose of avertin administered, in that movements were less frequent after large doses than after small, independent of the supplementary anesthetic used. However, restlessness was much less frequent or entirely absent in the presence of local anesthesia, so the nature of the supplement contributes significantly to this unsatisfactory postoperative reaction.

From 50 to 100 per cent of all restless patients (with the exception of those in the brain group) received medication (indicated in the charts by a plus symbol) postoperatively.

Nausea and Emesis.—A small percentage of patients in each of the special surgical groups showed this reaction postoperatively. The frequency was greatest in the gallbladder group and next greatest in the gynecological group. The major portion of the nauseated patients also vomited, but occasionally emesis occurred in the absence of nausea.

TABLE 2.—*Data in Relation to the Anesthetic Sequences*

Anesthetic Sequence	Number of Cases	Number of Patients Showing Pulmonary Complications	Number of Complications per Cent of Total
Pentobarbital sodium, morphine and nitrous oxide and oxygen, nitrous oxide, oxygen and ether, or ether	378	1	0.264
Avertin, morphine and nitrous oxide and oxygen, nitrous oxide, oxygen and ether or ether	317	6	1.89
Morphine, atropine, nitrous oxide and oxygen, nitrous oxide, oxygen and ether or ether*	505	11	2.18
Morphine, atropine and ether	185	5	2.7
Local, with and without morphine	341	3	0.88

* This group included the majority of poor anesthetic risks.

UNTOWARD REACTIONS IN THE ENTIRE GROUP

One patient became hysterical and another vomited shortly after the administration of avertin. Postoperatively several patients complained of headaches, 1 suffered from a nervous chill, 1 became irrationally talkative and 4 (0.94 per cent of the group studied in detail) showed marked respiratory depression. Two of those showing respiratory depression received morphine postoperatively.

The blood pressure fell to moderate shock levels (90 mm. of mercury or less) at some time during the course of anesthesia or on conclusion of the operative procedures in approximately 10 per cent of the total series, and became imperceptible in slightly less than half the patients showing such reactions. Low blood pressure observed preoperatively, i. e., after medication with avertin, as a rule returned to

normal or even above normal on administration of the general anesthetic, especially of nitrous oxide and oxygen. One half of the patients in whom shock reactions occurred were treated, usually with ephedrine (¼ grain [48.5 mg.]).

The frequency with which pulmonary complications ranging from definite bronchitis to atelectasis or pneumonia occurred during 1932 in a carefully studied group of general surgical cases with a series of anesthetic procedures is indicated in table 2.

Five deaths occurred in the group of 585 patients subjected to anesthetic and surgical procedures whose records were examined. One patient died one hour and a half after the removal of the major portion of one frontal lobe of the brain. The surgical procedures following which the other patients died were: an exploratory laparotomy; amputation of a leg; a gastric resection and the removal of an embolus. With the exception of the case in which a cerebral operation was performed, death occurred from ten hours to four days postoperatively. Avertin was not considered contributory to the fatal termination in any of the patients receiving the drug.

SUMMARY AND CONCLUSIONS

A general survey has been made of 1,831 records of anesthesias in which the patients were given morphine, atropine and avertin in doses of from 50 to 100 mg. (median 80 mg.) per kilogram of body weight, supplemented with several types of general anesthetics. The dose of the hypnotic was adapted to the age and general condition of the patient. Young patients (from 1 to 18 years) received maximal doses (90 to 100 mg. per kilogram). Aged patients as a rule received minimal doses. The optimal average adult dose of avertin appeared to be from 80 to 85 mg. per kilogram.

Ninety-two per cent of patients given premedication came to the operating room asleep. Occasionally (following medication with small doses as a rule) movements persisted. On arrival the patients were usually relaxed and, although satisfactorily analgesic, still responded to painful stimuli. The pulse rate was variable, and occasionally wide oscillations on either side of the normal rate were noted. The median rate increased slightly with small doses, but was either unchanged or slightly depressed by maximal doses. The extremes of age were associated with the least stability. The values of the blood pressure and pulse rate bore an inverse relation. The median blood pressure decreased 18 per cent, with a maximal range of from 5 above to 40 per cent below normal. Changes were minimal with the young and maximal with the aged patients. The respiratory rate was either unchanged or accelerated by medication; i. e., if a significant depression of respiration occurred the rate increased. The volume was rendered more shallow. The

minute volume was depressed in proportion to the dose of the hypnotic administered, and the percentile decrease varied from 22 per cent (with 70 mg. of avertin) to 40 per cent with maximal doses of the hypnotic. In exceptional cases, doses of 90 mg. reduced the minute volume more than 50 per cent.

Induction of anesthesia was rapid. From 80 to 85 per cent of the anesthesias were good; the remainder, fair or poor. Poor anesthesias were noted more frequently after small doses of avertin, and were more frequently observed with an ether supplement than with other general anesthetics. Movements occurred not infrequently in the course of local anesthesia following medication with avertin in doses as high as 90 to 100 mg. per kilogram. Patients in the thyroid, brain or gynecological groups responded less satisfactorily than did patients subjected to other types of operations. Young patients reacted better than aged ones and males somewhat better than females.

The pulse rate was accelerated from 10 to 40 per cent above the normal during anesthesia. The degree of change was variable, but grossly proportional to the dose of the hypnotic administered under constant conditions as to age and supplementary anesthetic.

The blood pressure increased during the course of operation and partially or completely compensated for the fall that occurred following premedication. The increase noted was greatest after minimal doses of avertin, and was of distinctly smaller magnitude in aged as compared with younger patients similarly medicated. The blood pressure of the thyroid group increased to a significantly greater degree than was observed in other surgical groups. The increase in diastolic pressure was usually of greater magnitude than the accompanying systolic change.

The respiratory rate increased from 30 to 60 per cent during anesthesia. The volume remained more shallow than normal. The respiratory depression apparent following premedication was partly counteracted by the anesthetic procedures. The margin of safety was narrowed, and the responsiveness to carbon dioxide was reduced. This disturbance diminished somewhat as the effects of avertin wore off. Postoperatively the respiratory rate remained slightly above normal for from one to two hours. The minute volume became either normal or approached the level at premedication. Exceptionally cyanosis developed.

Postoperative restlessness was observed in from 20 to 60 per cent of the patients, but was not troublesome from a nursing standpoint, although from 50 to 100 per cent of the restless patients received medication. The frequency with which restlessness occurred bore an inverse relation to the hypnotic dose administered. The complication was less frequent in aged than in younger persons. Little difference in this

respect was noted among the various surgical groups. At least part of the postoperative movements were due to the nature of the general anesthetic used, in that ether appeared to exaggerate the reaction, whereas movements were minimal in the presence of local anesthesia.

The duration of postoperative sleep bore little relation to the dose of avertin administered. The period of postoperative unconsciousness was significantly influenced by the nature of the anesthetic supplement and the duration and severity of the operative procedures. The duration was greatest with an ether supplement, and no sleep occurred after local anesthesia. The young and the aged patients appeared to be somewhat more sensitive to avertin than the normal adults.

Nausea and emesis occurred in approximately 20 per cent of the general surgical patients during the postoperative period. The frequency was greatest in the gallbladder group. The correlation of frequency was not close, but nausea and emesis appeared to be greater in females than in males and somewhat greater with small doses than with maximal doses of the hypnotic.

A moderate degree of renal damage occurred following the administration of avertin. Albumin (30 per cent frequency) and casts (7 per cent frequency) were observed in the specimens of urine taken twenty-four hours postoperatively. The majority of the specimens taken from forty-eight to seventy-two hours postoperatively showed no albumin or casts; exceptionally, traces persisted for several days. Traces of sugar were noted not infrequently, but were considered unimportant. However, 1 patient showed severe glycosuria postoperatively, and the condition continued for more than ten days.

Undesirable reactions following medication with morphine, atropine and avertin included a rather significant fall in the blood pressure and a definite depression of the respiratory volume, which occasionally was marked. If the depression was significant the rate became accelerated. The depression of respiration was apparent during the anesthesia in that the anesthetic margin was reduced. One patient became hysterical and another vomited shortly after the administration of the hypnotic.

Shock reactions of greater or less degree were observed in approximately 10 per cent of the patients either during the operation or during the postoperative period. The blood pressure became imperceptible in half of these and the patients required treatment.

The use of a morphine-atropine-avertin-supplementary anesthetic sequence reduced the frequency of pulmonary complications significantly as compared with a morphine-ether sequence. The frequency of pulmonary complications following the avertin sequence did not differ to a noticeable degree from that following a morphine-atropine-nitrous oxide, oxygen and ether sequence, especially when the greater number of poor operative risks in the latter group are taken into consideration.

The optimal anesthetic sequence, as judged by the infrequency with which undesirable side actions occurred and the significantly lower frequency with which pulmonary complications were observed as compared with any other anesthetic sequence tested, appears to be as follows: medication with pentobarbital sodium, morphine and atropine and the establishment of surgical anesthesia by means of a nitrous oxide, oxygen and ether supplement.

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ACUTE INTESTINAL OBSTRUCTION

IMMEDIATE AND LATE RESULTS IN A HUNDRED CONSECUTIVE CASES

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This article is based on an analysis of the immediate and late results in one hundred consecutive cases of acute intestinal obstruction in which operation was performed at the Reading Hospital from August 1925 to August 1933.

Intestinal obstruction or ileus is the term used to indicate a stoppage of the fecal current, this condition being secondary to some pathologic process within or without the intestine, which is the primary condition. If the primary condition is mechanical, there is a mechanical obstruction; if it is due to a nervous or toxic influence which paralyzes the intestines, it is a paralytic or adynamic ileus, and if it is due to a spasm or contraction of the intestinal wall, it is dynamic ileus.

By far the larger number of instances of obstruction are due to mechanical agents. In the present series the causative factor was mechanical obstruction, and in all the cases the obstruction was acute and complete. Cases of pyloric obstruction, carcinoma of the rectum, postoperative ileus and mesenteric thrombosis were not included.

The data covering the end-results were obtained by a questionnaire sent the patient, and the information was received from the patient, a member of the immediate family or the family physician. The questionnaire was sent one month after the last patient was discharged from the hospital.

CLINICAL DIAGNOSIS

The diagnosis is made largely on the basis of the history and the physical examination. Early diagnosis is not always easy. Usually, however, within a few hours, highly suggestive symptoms are present. Among these may be mentioned intermittent pains, nausea, vomiting, inability to pass gas, violent peristalsis and a failure of enemas to relieve the distress. The tighter the constriction is, the more sudden the attack. The pain usually becomes generalized, violent and continuous, with sharp exacerbations. The continuous pain is due to the constriction, the exacerbations to the colic of peristalsis as the intestine above the obstruction vainly lashes itself in its efforts to force material through the block. All the patients in this series had pain. Vomiting comes

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on soon after pain. At first, it is reflex. It is accompanied by nausea and soon by severe retching, which continues practically without relief, whether food is taken or not. Depending on the size of the block, the material vomited consists of, first, gastric contents, next, bilious matter, then, brown intestinal contents and, finally, material which is fecal in character. In the present series eighty-four patients vomited; in nine the symptom was not mentioned in the history, and in seven there was no vomiting. A prominent symptom of intestinal obstruction is the complete cessation of the passage of gas and feces. It is important to remember, however, that in the inception there may have been a passage of flatus, or even a bowel movement, owing to peristalsis emptying the intestine below the site of the obstruction. As time goes on, in

TABLE 1.—*Causes of Intestinal Obstruction*

Pathologic Process	Number of Cases	Number of Deaths	Mortality, per Cent
Hernia	49	16	32.6
Adhesions	19	7	36.84
Carcinoma of the intestine	13	8	61.54
Volvulus	5	2	40.0
Intussusception	4	3	75.0
Atresia of the intestine	2	2	100.0
Gallstones	2	1	50.0
Concretions	2	2	100.0
Metastatic growths	2	0	0.0
Meckel's diverticulum	1	0	0.0
Tuberculous peritonitis	1	0	0.0

spite of the great desire on the part of the patient for an evacuation, there is complete failure. Enemas are returned clear or require siphoning off.

A serious evil in the management of all acute abdominal disorders is the administration of morphine before the diagnosis has been made. The warning of intermittent colicky pain is silenced, the medication alters the symptoms and produces new symptoms and, worst of all, much valuable time is lost.

Other symptoms of the condition are a progressively anxious expression, pallor, rapid and weak pulse, diminished output of urine, which contains large amounts of indican, subnormal temperature, dry tongue and foul breath, tympanitis and collapse.

LABORATORY DIAGNOSIS

There is not much material available for laboratory diagnosis, nor is there time for it. Naturally, a routine urinalysis is imperative, and a blood count should also be done. Leukocytosis is absent in the early stage. Later, incident to the dehydration brought about by vomiting,

a high leukocyte count may be present, with similar increases in the hemoglobin and red blood cells.

Blood chemistry is only of prognostic and therapeutic value. Elevation of the blood urea, decrease in the plasma chloride and alkalosis occur regularly in high obstruction after about two days of vomiting, but are not early signs of acute intestinal obstruction. In low obstructions these changes are usually absent.

Roentgen examination following the administration of barium sulphate by mouth should never be done in these cases, for it aggravates the condition, and the diagnosis can be made without it. Recently, the "flat plate" of the abdomen has been employed. This was used originally by Schwartz,[1] in 1911. Case[2] introduced the procedure in this country about the same time. In many hospitals the procedure is a routine in all cases in which intestinal obstruction is suspected. The patient is given an enema, and the picture is taken with the patient

TABLE 2.—*Age Incidence in the Hundred Cases Reported*

Age	Number of Cases
Birth to 5 years	9
6 to 10 years	1
11 to 20 years	1
21 to 30 years	9
31 to 40 years	6
41 to 50 years	19
51 to 60 years	21
61 to 70 years	21
71 to 80 years	8
81 to 90 years	5

standing up or lying down, depending on his condition. Normally, there is not enough gas in the small intestine to be recognized in a roentgenogram. In obstruction of the small intestine, collections of gas can often be seen early. There are two types of intestinal outline: (1) a herring-bone appearance, due to the gas giving a feathery or slashed appearance to the intestinal loop, and (2) a ladder arrangement of the shadows of the intestinal coils, when the distended loops lie parallel. The latter appearance is pathognomonic of acute obstruction requiring immediate surgical intervention. The herring-bone aspect signifies a degree of hindrance which constitutes a serious menace to the patient, but which has, in some instances, been seen to appear and later disappear under nonsurgical treatment.

If an obstruction of the colon is suspected, a barium enema should be given to prove and to locate it.

In table 2 the age incidence in the cases in this series is shown.

1. Schwartz, G.: Die Erkennung der tieferen Dünndarmstenose mittels des Röntgenverfahrens, Wien. klin. Wchnschr. **24**:1386, 1911.

2. Case, James T.: Roentgenological Aid in the Diagnosis of Ileus, Am. J. Roentgenol. **19**:413 (May) 1928.

The ages from 21 to 70 years present the greatest incidence, the average age being 48.7 years. The youngest patient was 2 days old, and the oldest 85 years. There were fifty-three females and forty-seven males.

The hospital incidence was in a ratio of one to four hundred and three admissions.

DIFFERENTIAL DIAGNOSIS

The lesion for which early simple intestinal obstruction is probably most often mistaken is the "simple belly-ache," under which category one might list indiscretions in eating, abdominal allergic reactions and acute enterocolitis. In these, however, diarrhea is usually a prompt symptom, and vomiting is much less in the foreground than in obstruction. Even while the early vomiting of intestinal obstruction is reflex, as it is in gallstone or renal colic, the vomiting of obstruction is more frequent, more urgent and more copious than in other types of reflex vomiting.

Simple obstruction of the intestine causes colicky pain and colics, but these are often unaccompanied by local signs, in contradistinction to all the other colics of the abdomen, which are soon followed by local tenderness over the seat of the lesion. The pain of intestinal colic quickly reaches its acme, and falls rather abruptly, being sustained for only two or three minutes and recurring again after a free interval. The duration of the painful seizures attending distress in the gallbladder or kidney is much longer sustained.

Extra-abdominal lesions, such as syphilis of the central nervous system, tumors of the spinal cord, arthritis and tuberculosis of the spine, may cause rigidity of the abdominal muscles, but tenderness is usually absent. In the extra-abdominal lesions the pain is usually more continuous, and nausea and vomiting are not prominent. In the colics of gastric crises, other neurologic findings serve to identify the disease.

In strangulation obstruction a large number of conditions must necessarily be thought of in the differential diagnosis, including: all the abdominal colics, such as gallbladder and renal seizures; the inflammatory conditions, such as appendicitis, salpingitis, peritonitis and renal infections; pancreatic necrosis and diaphragmatic pleurisy, purpura and other cutaneous lesions, with hemorrhage into the intestinal wall, and torsion of other organs, especially cystic ovaries and even the testes. In the case of an ovarian cyst twisted on its pedicle, the stethoscope and the local examination serve to differentiate, and vomiting is usually less marked and even absent.

In many cases there is difficulty in arriving at an absolute definite diagnosis.

There is, however, one comforting fact, namely, that practically all the conditions with which acute intestinal obstruction is likely to be confused demand operation almost as imperatively as does intestinal obstruction.

When one waits until all the points in the differential diagnosis can be explained accurately the patient usually dies.

Twenty-five patients had abdominal operations previous to obstruction, but in five of these there was no logical causal relationship for the later diagnosis.

PROGNOSIS

In complete intestinal obstruction death is inevitable unless there is surgical intervention, and the longer surgical intervention is delayed, the smaller will be the patient's chance of recovery. Miller [3] stated that the mortality increases approximately 1 per cent with each hour of procrastination, and Moynihan said that any mortality over 10 per cent should be regarded as the "mortality of delay."

TABLE 3.—*Previous Operation in Patients with Intestinal Obstruction*

Operation	Number of Cases
Appendectomy (approximately one half drainage cases)	14
Laparotomy for trauma	2
Panhysterectomy for a malignant process	1
Cholecystectomy	2
Inguinal hernia	2
Exploratory laparotomy and appendectomy	1
Bilateral salpingectomy and appendectomy	1
Ovarian cyst and appendectomy	1

LEVEL OF OBSTRUCTION

It is generally recognized that obstructions of the colon are less fulminating than those of the small intestine. Furthermore, it is also true that obstructions high in the small intestine are more rapidly fatal than those situated lower. Of course, if interference with the mesenteric circulation is present, death will occur as quickly in one situation as in another, as a result of the infarction of the intestine. In the present series the small intestine was the site of the obstruction in seventy-seven instances, the large intestine in twenty-one cases and both in two instances.

3. Miller, C. Jeff.: A Study of Three Hundred and Forty-Three Surgical Cases of Intestinal Obstruction, Ann. Surg. **89**:91, 1929.

CAUSE OF DEATH IN ACUTE INTESTINAL OBSTRUCTION

Much experimental work has been done to show the exact cause of death in acute intestinal obstruction, and numerous theories have been advanced. In general the conclusions fall into three groups:

1. Invasion of the body by bacteria from the damaged intestine. This obstruction is often accompanied by peritonitis and organisms in the blood. However, death often occurs without peritonitis, and cultures from the blood, liver, spleen and other organs are sterile.

2. The nervous reflex theory has been advanced as the cause of death. Thus, in volvulus, especially of a large portion of the intestine, reflex shock seems to play a great part. Whenever the blood supply to the intestine is interfered with, the symptoms are fulminating and there are early necrosis and perforation.

3. Most investigators now agree that the symptoms of obstruction are due to the absorption into the system of poisonous material from

TABLE 4.—*Mortality In Relation To Anesthesia*

Type of Anesthesia	Number of Cases	Number of Deaths	Mortality, per Cent
Local (procaine hydrochloride)	11	3	27.27
Nitrous oxide and ether	32	9	28.12
Nitrous oxide	10	3	33.3
Spinal	15	6	40.0
Ether	10	5	50.0
Spinal and general	18	11	61.11
Local and general	4	4	100.0

the obstructed intestine. This is the chemical poison or toxic theory. The possible routes by which the toxin enters the circulation are through the peritoneal cavity via the lymphatic stream or directly into the portal blood. There is some question as to whether the toxin is found in the lumen or in the mucosal cells. It has been shown experimentally by Scholefield [4] that bacteria and a highly organized mucosa are necessary factors. Furthermore, intra-intestinal pressure and time are important elements in the production of this toxin. Whipple [5] and Stone isolated, by precipitation with a solution of 95 per cent alcohol, a substance which resembled proteose. This could be redissolved in water, and was precipitated by half saturation with ammonium sulphate. One hundred milligrams of the substance was sufficient to kill a dog weighing 15 pounds (6.8 Kg.).

Sir Frederick Treves pointed out in his book on intestinal obstruction that the final outcome in these cases was not primarily dependent on the actual stoppage of the flow of material along the intestinal tract,

4. Scholefield, Bernard G.: Guy's Hosp. Rep. **77**:160 (April) 1927.

5. Whipple, A. O.: Safety Factors in the Treatment of Acute Intestinal Obstruction, Boston M. & S. J. **197**:218, 1927.

but rather on the absorption of toxic products from the disordered intestine, resulting in septic infection of the whole body. He stated that the subjects of acute intestinal obstruction die for the most part with the phenomena of septic poisoning, and if a certain stage has been passed, the mere relief of the obstruction does not save life.

Table 4 suggests that a simple type of anesthesia, such as local, nitrous oxide or spinal anesthesia, is less hazardous than a combination of any one of these with ether anesthesia.

TREATMENT

The essence of the treatment of acute intestinal obstruction is early diagnosis and early surgical intervention. When the decision to operate has been made, no time should be lost in preoperative preparation. During the time that preparations are being made in the operating room, the patient's stomach should be evacuated by lavage, and dextrose and physiologic solution of sodium chloride should be given intravenously and subcutaneously to restore the fluid balance and replace the lost chlorides.

When there is early surgical intervention, the choice of anesthetic is not so important; however, to administer inhalation anesthesia to a patient who has regurgitant vomiting and considerable distention, even though the stomach has been emptied, adds hazard to the operation. Spinal anesthesia is ideal.

The surgical procedure is based on its relation, not only to the pathologic condition present, but also to the condition of the patient. No more should be done than the patient's condition warrants. It is here that surgical judgment and experience count a great deal. In some instances, a complete operation may be performed, that is, finding and releasing the obstruction and restoring the continuity of the intestine, whether this is done by mere release of the constricted intestine or by resection.

In other cases, drainage of the intestine by enterostomy, exteriorization, cecostomy and colostomy is all that may be done with safety. In the latter cases, a secondary operation is often performed later.

The postoperative treatment is as important as the diagnosis and the operation, and varies in each instance. Three things are of paramount importance: The stomach must be emptied by lavage if necessary. Lost body fluids must be replenished in the form of hypertonic saline and dextrose solution. The patient's general condition must be guarded, with particular attention to the cardiovascular system.

RESULTS OF OPERATION

Immediate.—In my series fifty-nine patients survived and forty-one died. Of the forty-one who died, all had preoperative vomiting except

four. The four who did not have preoperative vomiting had a strangulated intestine at the time of the operation, and two required intestinal resections. There were twenty-five postmortem examinations. In most of the twenty-five, a continuation of the findings at operation was found, namely, peritonitis and gangrene of the intestine. In four cases there was massive postoperative pneumonia, in three, marked postoperative adynamic ileus, and one patient died on the operating table fifteen minutes after nitrous oxide anesthesia was started. The last mentioned patient had been toxic, with a diagnosis of strangulated inguinal hernia,

TABLE 5.—*Mortality In Relation To Operative Procedure*

Procedure	Number of Cases	Mortality
Repair of hernias	46	14
Release of adhesions	17	5
Reduction of volvulus and intussusception	5	1
Resection	9	6
Resection and drainage of the intestine	9	6
Enterotomy	4	3
Enterostomy	1	1
Cecostomy	4	3
Colostomy	4	1
Obstruction not found	1	1

TABLE 6.—*Comparative Mortality of Series of Various Authors* *

Series	Mortality, per Cent
Cornell: Ann. Surg. **95**: 816, 1932	51.48
Deaver and Ross: Ann. Surg. **83**: 571, 1926	42.0
Finney: Surg., Gynec. & Obst. **32**: 402, 1921	36.0
Koslin: Ann. Surg. **95**: 821, 1932	38.38
McIver: Arch. Surg. **25**: 1008, 1932	31.0
Miller [3]	60.9
Rentschler	41.0
Seelaus: Pennsylvania M. J. **35**: 17, 1931	53.0
Vidgoff: Ann. Surg. **95**: 801, 1932	51.48

* The statistics were not all based on the same premises.

and had vomited for four days prior to operation, having refused to permit surgical intervention. One died of a Bacillus Welchii infection.

Of the sixteen cases in which postmortem examination was not permitted, twelve died on the day of the operation. Four died following extensive intestinal resection; two others had gangrenous and necrotic intestines, but in neither case did the patient's condition warrant resection. Three patients who had intussusception had blood in the stool for more than forty-eight hours, and the abdomen was markedly distended prior to the operation; one refused to permit operation until it was practically too late and one died with the clinical diagnosis of bronchopneumonia seven days after the operation. Three patients were 80 years, or more, of age.

Late.—Forty-seven of those who survived stated that they are generally well; however, four have incisional hernias. Three had minor operations, irrespective of the original condition, and two had major operations, appendectomy and radical amputation of the breast for carcinoma. One woman had a hernia at the site of the operation, which was cured by operation, and at the end of two years had no complaint. Another also had an incisional hernia with intestinal obstruction which was cured by operation, but again a hernia resulted, which was repaired a second time; a year and a half after her third operation she was in excellent condition.

Two, who had a malignant process in the intestine, are still living; in one, fourteen months after a colostomy, the primary growth was inoperable, and the other was generally well and working one year after the excision of the intestinal growth. Several of the aged have afflictions such as myocardial degeneration.

Twelve are dead. Three died of a malignant process in the intestines. Two died as a result of intestinal obstruction caused by a metastatic malignant process. Two died of tuberculosis; one, of pulmonary tuberculosis six years after the operation for intestinal obstruction, and the other, two months after the operation of a continuation of tuberculous peritonitis. Another died following an operation for recurrence of the intestinal obstruction; both times the obstruction was due to adhesions. The four other deaths were a result of old age, one, a year, two, two years, and one, three years later.

CONCLUSIONS

1. The mortality following acute intestinal obstruction is too high.

2. The only way to reduce the mortality is to relieve the obstruction before it is too late.

3. Waiting for a perfect and detailed preoperative diagnosis is the cause of death in most of the fatal cases.

4. In a case of early obstruction, a complete operation can usually be safely performed. In late obstruction, one had better perform the operation in stages, rather than take too much chance on the life of the patient.

5. Death is due to three primary factors: obstruction of the fecal current, necrosis of the intestine and the production and absorption of toxins.

SHOCK

FURTHER STUDIES WITH PARTICULAR REFERENCE TO THE EFFECTS OF HEMORRHAGE

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In many of the experiments on shock which I have previously reported, sodium barbital was used as the anesthetic. Parsons and Phemister used ether or sodium barbital or either of these supplemented by morphine in most of their experiments. Similar findings were reported [1] by the two groups of investigators. Sodium barbital in the dosages employed in these experiments produces unconsciousness, an acceleration of the pulse rate, a decline in the pulse pressure, occasionally a drop in the arterial blood pressure, infrequently early death and frequently a moderate amount of capillary congestion and hemorrhage in some of the organs of the body. Most of these changes are produced by any agent which will produce profound anesthesia for a number of hours. It is unfortunate that the experimental production of a great many pathologic conditions has for humane reasons to be accompanied by a complicating factor such as an anesthetic. However, the finding that there was a loss of a sufficient part of the blood volume into the injured part to account for the low blood pressure in the experiments in which an extremity was traumatized, despite the fact that the anesthesia was profound, would seem to indicate that the circulatory systems of the animals were not necessarily markedly impaired by the anesthetic agents. In order to obtain further information, additional experiments were performed which are reported in the present paper.

The initial experiments consisted of studies of the alterations in the blood and various tissues of the body that are produced by profound anesthesia. This was followed by experiments in which shock was produced by traumatizing an extremity, several different anesthetics being used, and the local loss of fluid, as well as the changes in the

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From the Department of Surgery of Vanderbilt University.

This study was aided by a grant from the Fluid Research Fund of the Rockefeller Foundation.

1. Blalock, Alfred: Experimental Shock; the Cause of the Low Blood Pressure Produced by Muscle Injury, Arch. Surg. **20**:959 (June) 1930. Parsons, Eloise, and Phemister, D. B.: Haemorrhage and Shock in Traumatized Limbs, Surg., Gynec. & Obst. **51**:196 (Aug.) 1930.

tissues, was studied. The effects of a low blood pressure produced by other means, as by injecting histamine and acetylcholine and by causing an increased intrapericardial pressure, were next determined. These experiments led to others in which the effects of maintaining the blood pressure at a low level by hemorrhage were studied. The results of the experiments on hemorrhage appear to be the most significant, and this paper deals primarily with them.

Probably the most generally accepted distinctive characteristics of shock and of hemorrhage are summarized in a recent editorial in *The Journal of the American Medical Association*,[2] as follows:

> A recent paper [3] indicates that two criteria are available to distinguish between shock and hemorrhage: In shock the blood becomes more concentrated, as shown by specific gravity, hemoglobin and erythrocyte count; following hemorrhage, dilution of blood occurs. In shock there are widespread capillary dilatation of the viscera, congestion accompanied by edema, and petechial hemorrhages; following hemorrhage the tissues are anemic. The differentiation of hemorrhage and shock is of more than academic importance. It is well known that recovery follows the introduction of physiologic solution of sodium chloride into the circulation of patients suffering from the simple loss of blood. The futility of this procedure in shock has been proved beyond question. The increased permeability of the capillaries, which is a characteristic feature of shock, allows saline solution to escape rapidly into the tissues. Solutions containing acacia or dextrose have been found more effective than saline solutions but not so effective as the transfusion of blood. Even the latter is ineffective in profound shock.

The results obtained in the previous studies on traumatic shock by me and by Parsons and Phemister so clearly indicated that this condition could be attributed solely to the actual loss into the injured area of the various constituents of the blood that it seemed reasonable to believe that the same condition could be produced by hemorrhage alone.

GENERAL METHODS

Dogs were used in all of the experiments. They were maintained free of pain by the use of local or general anesthetics. A cannula that was connected to a mercury manometer was placed in the femoral or carotid artery for the determination of the blood pressure. Hematocrit determinations on venous blood were performed in duplicate by the use of Van Allen tubes. Immediately following the death of the animals, the abdominal and thoracic cavities were opened, and the organs were examined. The weights of the heart, lungs, liver, intestinal tract, exclusive of the stomach and esophagus, kidneys and spleen were determined. After removal of these organs without having ligated the blood supply, the quantity of free blood that remained in the pleural and peritoneal cavities was determined. Microscopic sections of tissues removed from the cardiac, pulmonary, hepatic, duodenal, renal, splenic, pancreatic, suprarenal and skeletal muscle were prepared and examined.

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2. Shock, editorial, J. A. M. A. **100**:46 (Jan. 7) 1933.

3. Moon, V. H., and Kennedy, P. J.: Pathology of Shock, Arch. Path. **14**:360 (Sept.) 1932.

In the experiments in which an extremity was traumatized, the loss of fluid into the injured area was determined by a method that has previously been described.[1] In other experiments, histamine and acetylcholine were injected subcutaneously at frequent intervals in amounts sufficient to maintain the blood pressure at a low level. An increase in the intrapericardial pressure was produced by introducing fluid through a cannula that was anchored into an opening in the pericardium by the method employed by Cannon.[4] The blood pressure can be reduced to any desired level by this procedure. Most of the experiments in which the effects of hemorrhage were studied were performed without general narcosis. Pain was prevented by the injection of procaine hydrochloride at the sites where cannulas were introduced for the determination of the blood pressure and for the removal of blood. A few of the animals became restless during the course of the observations and were given small dosages of morphine. The results were the same in the experiments in which procaine hydrochloride alone was used as in those in which the procaine hydrochloride was supplemented by a small amount of morphine. The experiments in which the blood pressure was maintained at a low level as a result of hemorrhage may be divided into five groups. In the first group, blood was withdrawn slowly from the femoral artery until the systolic pressure was reduced to less than 70 mm. of mercury. When the pressure rose above this level, additional blood was removed. After a sustained decline in the arterial pressure to less than 70 mm. was produced, the animal was allowed to die without further removal of blood. The desired condition was to have the animal live with a low blood pressure as long as possible, and it required a great deal of care in the removal of blood in order to do this successfully. In the remaining four groups of experiments, the blood pressure was reduced to a low level by hemorrhage, and it was maintained fairly stationary at this low point by the further removal of blood, if the pressure rose, or by the introduction of blood, if the pressure fell. It is to be emphasized that large amounts of blood were usually not introduced at one time. An attempt was made to inject just enough to keep the pressure from falling to too low a level. In one group of experiments the blood that was removed from the animal and subsequently injected was prevented from clotting by defibrination; in another group it was mixed with sodium citrate, and in still another it was placed in a solution of heparin. In the fifth group of experiments, the blood was transfused by the direct method from a suitable donor.

OBSERVATIONS

Normal Controls.—The sudden death of seven normal animals was produced in order that the weights of the organs might be determined, and that normal tissues might be obtained for study. In some instances death was caused by electrocution and in others by opening the pleural cavity of animals anesthetized for a few minutes by ether. The average weights of the organs are given in the table, as are those obtained in the remaining groups of experiments. The average quantity of blood remaining in the pleural and peritoneal cavities after the removal of the organs equaled in terms of body weight 5.93 per cent.

Effects of Sodium Barbital Anesthesia.—Six experiments were performed in which the effects of barbital anesthesia were studied. The

4. Cannon, W. B.: Traumatic Shock, in Surgical Monographs, New York, D. Appleton and Company, 1923, vol. 1, p. 63.

anesthetic was injected intravenously in the dosage of 0.3 Gm. per kilogram of body weight. The administration of barbital was followed by an increase in the pulse rate and a decrease in the pulse pressure. The average duration of the control experiments on the effects of barbital anesthesia alone was six hours and thirty-two minutes. The average mean arterial blood pressure before the injection of barbital was 133 mm., and at the completion of the experiments, 121 mm. In some instances the concentration of the red blood cells increased, and in others it diminished. Death of the animals was produced in some experiments by electrocution and in others by the opening of the pleural cavity.

Weights of Organs

Experimental Condition	Number of Experiments	Average Weight of Dogs, Kg.	Weight of Organs in Grams per Kilogram of Body Weight							
			Right Lung	Left Lung	Heart	Liver	Spleen	Right Kidney	Left Kidney	Intestinal Tract
Control	7	11.2	5.43	3.81	7.80	29.48	1.86	2.49	2.66	41.26
Ether control	5	13.3	5.38	3.62	6.71	25.59	2.85	2.50	2.47	34.85
Barbital control	6	16.3	5.50	3.75	7.73	27.15	2.99	2.83	2.91	33.44
Ether and trauma	10	14.3	4.32	3.23	7.34	28.29	3.12	2.74	2.79	35.69
Barbital and trauma	12	13.8	5.29	3.90	7.44	29.76	2.84	2.76	2.85	36.57
Ether and hemorrhage	9	12.1	4.83	3.48	7.31	29.69	3.17	2.56	2.62	36.80
Barbital and hemorrhage	8	13.5	4.64	3.20	7.09	27.24	2.86	2.41	2.47	31.59
Spinal anesthetic and trauma	5	14.3	5.21	3.80	7.48	31.73	3.54	2.82	2.80	38.26
Spinal anesthetic and hemorrhage	5	15.2	5.06	3.59	7.46	27.67	3.08	2.28	2.35	32.40
Ether and histamine	5	10.8	4.80	3.35	7.01	33.45	2.58	2.67	2.67	35.50
Barbital and histamine	6	15.8	5.01	4.06	7.71	37.06	3.30	2.62	2.75	36.53
Hemorrhage; no replacement	7	13.9	4.48	3.44	7.03	27.26	3.33	2.54	2.64	33.26
Hemorrhage; replaced defibrinated blood	9	13.05	4.78	3.31	7.17	32.11	3.54	2.69	2.91	36.85
Hemorrhage; direct transfusion	4	9.2	5.04	3.88	8.13	33.29	3.65	2.85	2.91	37.56
Acetylcholine	2	10.06	4.62	3.31	5.99	29.78	3.63	2.63	2.74	40.98
Increased intrapericardial pressure	2	12.9	5.08	3.80	6.34	29.09	4.00	3.37	3.43	36.71

Autopsies revealed slight reddening with a small amount of blood in the lumen of the intestinal tract in four of the six experiments. The lungs presented a few hemorrhagic areas in five experiments, and the wall of the gallbladder was somewhat thickened in five. The most marked microscopic alterations in the tissues that were removed for study were: (1) There were moderate capillary congestion and slight hemorrhage in the suprarenal glands, with a great many polymorphonuclear leukocytes in the cortex surrounding the medulla; (2) the small intestinal tract showed slight congestion and hemorrhage; (3) there was slight congestion of the vessels of the heart; (4) the kidneys revealed moderate capillary congestion and dilatation, and (5) there were a moderate amount of congestion and dilatation of the pulmonary capillaries, and atelectasis. The average quantity of blood remaining in the pleural and peritoneal cavities following the removal of the organs equaled 5.2

per cent of the body weight or approximately half of the estimated total blood volume.

Effects of Ether Anesthesia.—Five experiments were performed in which the effects of ether anesthesia administered by inhalation were studied. The depth of anesthesia was such that the muscles were well relaxed. The eye reflexes were not abolished. Ether caused an increase in the pulse rate and a decrease in the pulse pressure. The average duration of the studies was six hours and twenty-two minutes. The average mean arterial blood pressure before the administration of ether was 138 mm., and at the completion of the observation period it was 105 mm. The concentration of the red blood cells increased in all of the experiments. The average hematocrit reading changed from 40.6 per cent during the control period to 49.9 per cent at the conclusion. Postmortem examinations showed scattered hemorrhages in the jejunum and ileum. The mucous membrane of the intestinal tract except at the site of the hemorrhage was essentially normal in color. The lungs presented one or more areas into which hemorrhage had occurred. The liver in some instances was dark. In one experiment there was a great deal of hemorrhage in the endocardium of the left ventricle. On microscopic examination, the following changes were observed: A moderate amount of congestion and hemorrhage were present in the suprarenal glands. A few of the cells of the medulla were undergoing necrosis. A moderate number of polymorphonuclear leukocytes were present in the cortex. The duodenum showed moderate capillary congestion and dilatation. There were slight capillary congestion and hemorrhage in the cardiac muscle in some experiments. The gallbladder was slightly edematous in a few instances, and there was capillary congestion. There were capillary congestion and dilatation in the kidneys. The liver showed vacuolation, a good deal of hemorrhage and congestion and a moderate number of polymorphonuclear leukocytes. The lung was partially atelectatic, and capillary dilatation and congestion were present. A moderate amount of congestion was present in the pancreas. The spleen showed focal necrosis of the lymphoid tissue. The average amount of blood remaining in the pleural and peritoneal cavities following the removal of the organs equaled 4.2 per cent of the body weight.

In summary, the alterations in the tissues that were produced by ether anesthesia were definitely more marked than those found in experiments in which sodium barbital was used as the anesthetic.

Barbital and Hemorrhage.—The animals were anesthetized by the usual amount of sodium barbital, and three hours later the removal of blood in small amounts at frequent intervals was begun. This was continued until death resulted. Eight such experiments were performed.

The average duration of the studies was five hours and forty-one minutes. The average amount of blood removed in terms of body weight equaled 4.21 per cent. The blood pressure did not remain at a low level for more than an hour in any of the experiments. The concentration of the red blood cells increased in five experiments and decreased in three. The average hematocrit readings at the beginning and end of the experiments were 46.8 and 49, respectively. The average amount of blood left in the pleural and peritoneal cavities after the removal of the organs equaled 1.34 per cent of the body weight. The changes in the tissues will not be described in detail. It suffices to state that they were slightly more marked than those found in the experiments in which the effects of barbital alone were studied. As has been stated, the blood pressure was at a low level for only a short while preceding the death of the animals.

Barbital and Trauma.—Twelve experiments were performed in which one of the posterior extremities was traumatized after the animals were anesthetized with barbital. The amount of barbital used was 0.3 Gm. per kilogram of body weight. The average time elapsing between the initiation of the trauma and death was five hours and twenty-eight minutes. The average difference in the weights of the traumatized and nontraumatized extremities in terms of body weight was 4.5 per cent or a little less than half of the estimated total blood volume. The average length of time that the blood pressure remained at a low level before death took place was approximately one and one-half hours. An increase in the concentration of the red blood cells occurred in nine experiments, and a decrease was found in the remaining three. The average amount of blood remaining in the cavities after the removal of the organs was 2 per cent of the original body weight. The gross and microscopic changes in the tissues were slightly but definitely more marked than those encountered in the experiments on the effects of barbital alone. Early necrosis of some of the cells of the suprarenal glands, duodenum, liver and spleen was observed. In several of the experiments there was a great deal of hemorrhage into the intestinal tract.

Ether and Hemorrhage.—Nine experiments were performed in which blood equaling 1 per cent of the body weight was removed at one hour intervals from dogs anesthetized by ether. This was continued until death resulted. The average duration of the experiments was three hours and forty-one minutes. The average loss of blood resulting in death in terms of body weight was 4 per cent or less than half of the total blood volume. The usual length of time that the blood pressure remained at a low level was slightly more than one hour. There was a decrease in the concentration of the red blood cells in six experiments

and a slight increase in the remaining three. The blood remaining in the pleural and peritoneal cavities after the removal of the organs equaled 1.7 per cent of the body weight. The gross and microscopic alterations in the tissues were not quite so marked as those found in the experiments in which the effects of ether alone were studied. It is to be remembered that the latter experiments were of longer duration. In several experiments there were a few small hemorrhagic areas in the intestinal tract.

Ether and Trauma.—Ten experiments were performed in which one of the posterior extremities of dogs anesthetized by ether was traumatized. The experiments were continued until death occurred. The average duration was five hours and ten minutes. The average difference in the weights of the injured and noninjured extremities in percentage of body weight was 4.46. The duration of the low blood pressure preceding death varied from thirty minutes to three hours. There was an increase in the concentration of the red blood cells in eight experiments and a dilution in the remaining two. The blood remaining in the pleural and peritoneal cavities after the removal of the organs equaled 1.7 per cent of the body weight. In several of the experiments there were many hemorrhagic areas with free blood in the intestinal tract. The suprarenal glands, liver and duodenum showed on section in some instances a moderate amount of hemorrhage and congestion and slight necrosis of the cells. On the whole, the alterations were slightly more marked than those encountered in the experiments in which the effects of ether alone were studied.

Spinal Anesthesia and Hemorrhage.—Spinal anesthesia was produced in this and in the subsequent group of experiments by the injection of 1 per cent procaine hydrochloride into the spinal canal in the lumbar region. A small amount of morphine was given subcutaneously previous to the injection of procaine hydrochloride. If a definite decline in the blood pressure followed the injection of the drug, the effects of hemorrhage or of trauma were not studied, since the tolerance to either of the procedures is markedly affected by a low blood pressure. One animal died one hour after 2 cc. of procaine hydrochloride had been injected into the spinal canal. No blood was removed, and no trauma was produced. It was observed at autopsy that the duodenum was markedly reddened and that the jejunum, ileum and large intestine were reddened to a lesser extent. The liver was dark. Rather marked alterations were found in the organs on microscopic study. The concentration of the red blood cells was increased.

Five experiments were performed in which the effects of spinal anesthesia and hemorrhage were studied. Blood equaling 1 per cent of the body weight was withdrawn at hourly intervals until death resulted.

The average duration of the experiments was four hours and thirteen minutes. The average amount of blood removed in terms of body weight was 4.8 per cent or approximately half of the total volume. The concentration of the red blood cells decreased in two experiments, remained the same in two and increased in one. The blood remaining in the pleural and peritoneal cavities after the removal of the organs equaled 1.25 per cent of the body weight. The mucous membrane of the intestinal tract was found to be very red in two of the experiments and slightly red in two others. Microscopic examination showed capillary congestion in most of the organs and hemorrhage in some.

Spinal Anesthesia and Trauma.—Five experiments were performed in which one of the posterior extremities was traumatized under spinal anesthesia. The average duration of the experiments was six hours and fifty minutes. The average difference in the weights of the traumatized and nontraumatized extremities equaled 4.45 per cent of the body weight. The blood pressure remained at a low level prior to death for varying periods. The red blood cells became more concentrated in all of the experiments. The average quantity of blood in the cavities after the removal of the organs equaled 1.53 per cent of the original body weight. The mucous membrane of the intestinal tract and the duodenum in particular was moderately red in all of the experiments. The microscopic alterations in the tissues were slightly more marked than those found in the experiments in which hemorrhage was carried out under spinal anesthesia. The changes were probably a little less marked than those found in the experiments in which trauma was produced in animals anesthetized by barbital or ether.

Barbital Anesthesia and the Injection of Histamine.—Six experiments were performed in which histamine was injected subcutaneously into dogs anesthetized by barbital. The average duration of the experiments was five hours and twenty-six minutes. The blood pressure was maintained depressed below its normal level during this time, and it was kept at a low level for approximately two hours. The red blood cells became more concentrated in all of the experiments. The average quantity of blood remaining in the pleural and peritoneal cavities after removal of the organs was 3.56 per cent of the body weight. Reddening of the skin was observed in most of the experiments. The vessels of the intestinal tract became very prominent. At autopsy, the mucous membrane of the small intestines was found to be quite reddened, and in some instances free blood was present in the lumen. The microscopic alterations in the tissues were slightly more marked than those found in the experiments on the effects of barbital alone or ether alone. Certainly the difference was not great. The most evident difference was in the

liver, where it seemed that the administration of histamine resulted in greater changes.

Ether and Histamine.—Five experiments were performed in which the effects of the injection of histamine into animals anesthetized by ether were studied. The results were practically identical with those obtained in the experiments in which the dogs were anesthetized with barbital and in which histamine was injected.

The changes that are noted following the injection of histamine are not dependent on the associated anesthesia. This was demonstrated in one experiment in which only local anesthesia was used. The changes in the tissues were marked.

Effects of the Injection of Acetylcholine.—Two experiments were performed in which acetylcholine was injected intramuscularly into dogs narcotized by 0.033 Gm. of morphine. Sufficient acetylcholine was injected at frequent intervals to keep the mean arterial blood pressure at approximately 75 mm. for three hours. At the end of this time, the animals were killed. There was a marked increase in the concentration of the red blood cells. The blood remaining in the cavities after the removal of the organs equaled 3.46 per cent of the body weight. In both experiments reddening of the mucous membrane and hemorrhage into the intestinal tract were observed. In one of these the mucous membrane was beefy red in appearance. The liver showed a dark discoloration, and the wall of the gallbladder was thick and edematous. Microscopic study showed capillary congestion in all of the tissues studied except the skeletal muscle. There was hemorrhage into the liver and small intestines, and necrosis of some of the cells of the liver, duodenum and spleen.

Effects of Increased Intrapericardial Pressure.—Two experiments were performed in which the blood pressure was reduced by introducing fluid under pressure into the pericardial cavity. The animals were given a preliminary injection of morphine. Ether and artificial respiration were administered during the time that the cannula was being introduced into the pericardium. As soon as the chest was closed tightly, they were discontinued. The mean arterial blood pressure was maintained slightly below 70 mm. for three hours. At the completion of this time, the animals were killed. There was a marked increase in the concentration of the red blood cells. The average quantity of blood remaining in the pleural and peritoneal cavities after the removal of the organs equaled 4.74 per cent of the body weight. Autopsy in one experiment showed marked reddening of the mucous membrane of the duodenum and the upper ileum; the gallbladder wall was thick and edematous, and there was hemorrhage in the endocardium. In the other experiment, the mucous membrane of the intestinal tract was beefy red,

and there was free blood in the lumen. The lungs and liver showed hemorrhagic areas, and the wall of the gallbladder was thick and edematous. The most marked changes on microscopic examination were observed in the duodenum and liver, where there were capillary congestion, hemorrhage and necrosis. The alterations in the suprarenal glands were surprisingly minor in degree.

Effects of Hemorrhage Without Transfusion.—Seven experiments were performed in which blood was removed in small amounts at frequent intervals until the mean arterial pressure was approximately 70 mm. If the blood pressure rose, additional blood was removed. The animal was allowed to die as a result of the removal of blood with the idea in mind of having the blood pressure remain at a low level as long as possible. No general anesthetic was used in these experiments, and pain was prevented by the injection of procaine hydrochloride at the sites where the cannulas were introduced into the blood vessels. The average duration of the experiments was six hours but the greater part of the time was consumed in producing a decline in the pressure from which recovery would not result. The interval elapsing between the time of the last removal of blood and of death averaged only one hour and twenty-six minutes. Although the blood pressure did not remain at a low level for an extended time, the mean arterial pressure and the pulse pressure were definitely lessened throughout the experiments. The average amount of blood removed in the different experiments equaled 4.3 per cent of the body weight. The average quantity of blood remaining in the pleural and peritoneal cavities after the removal of the organs equaled 1.48 per cent of the body weight. There was a decrease in the concentration of the red blood cells in five experiments and an increase in two. In two experiments blood-stained material was passed from the rectum. In another, vomiting occurred two hours following the beginning of the experiment.

Autopsies were performed immediately following death. The mucous membrane of the intestinal tract was redder than normal in all of the experiments and blood-stained material was present in the lumen of the intestines in six of the seven experiments. The duodenum and jejunum presented the most marked alterations, but in some instances the ileum and large intestines showed reddening and hemorrhage also. Hemorrhagic areas were present in the lungs in some experiments. The following changes were observed on microscopic examination: The suprarenal glands showed fairly marked capillary congestion and hemorrhage and necrosis of some of the cells. Many polymorphonuclear leukocytes were located in the cortex surrounding the medulla. Slight vacuolation was present. The duodenum showed dilatation and thrombosis of capillaries, hemorrhage and necrosis of some of the mucous

membrane. There were slight hemorrhage and capillary congestion in the heart muscle. The skeletal muscle was essentially normal. Capillary congestion and dilatation were present in the kidneys. The liver showed capillary congestion, hemorrhage and necrosis of the liver cells. The location of the necrosis was variable. Atelectasis and capillary congestion were present in the lungs. There was a moderate amount of capillary congestion in the pancreas. The spleen showed hemorrhage into and some necrosis of the malpighian bodies.

Effects of Hemorrhage and of Autotransfusion with Defibrinated Blood.—Nine experiments were performed in which the blood pressure was reduced to a low level by hemorrhage and in which death was postponed by introducing blood when the blood pressure reached an extremely low level. The blood that was removed from the animals was defibrinated and strained through linen and kept at body temperature. Procaine hydrochloride was used at the sites where the cannulas were introduced. In four of the experiments, the animals were given 0.016 Gm. of morphine. No evidence of a reaction as a result of the introduction of blood was obtained in any of the experiments. The average amount of blood removed in the different experiments equaled 4.58 per cent of the body weight, and the average quantity replaced equaled 1.62 per cent of the body weight. In two of the experiments all of the blood that was removed was reintroduced, and yet the animals died. The average duration of the experiments was four hours and forty-four minutes. The blood pressure remained at a low level during the greater part of the duration of all of the experiments. These studies were of shorter duration than those reported in the previous group in which no blood was replaced, but the blood pressure remained at a low level for a longer time in the present experiments. There was an increase in the concentration of the red blood cells in four experiments and a decrease in five. The average quantity of blood remaining in the pleural and peritoneal cavities after the removal of the organs equaled 2.28 per cent of the body weight.

The alterations in the tissues will not be described in detail. They were definitely more marked than those encountered in the last group of experiments in which blood was removed and none was replaced. This difference is probably due to the fact that the blood pressure remained at a low level for a longer time in the present studies, or possibly the defibrinated blood resulted in alterations.

Effects of Hemorrhage and of Autotransfusion with Blood Collected in a Solution of Heparin.—Three experiments were performed in which the blood that was removed was placed in a solution of heparin to prevent it from clotting. When the blood pressure reached a low level, the heparinized blood was injected intravenously. Two of the experi-

ments were unsatisfactory in that a severe reaction followed the introduction of the blood. The results in the remaining experiment were approximately the same as those obtained in the studies in which defibrinated blood was injected.

Effects of Hemorrhage and of Autotransfusion with Blood Collected in a Solution of Sodium Citrate.—Four experiments were performed in which the blood that was removed was collected in a 2.5 per cent solution of sodium citrate. This blood was injected intravenously when the blood pressure reached a low point. A fairly severe reaction was associated in two of the experiments with the giving of the blood, and these studies were discarded. The blood pressure remained at a low level for five hours in one of the remaining experiments and for seven hours in the other. All of the blood that was removed was replaced. There was a marked increase in the concentration of the red blood cells. The average amount of blood remaining in the pleural and peritoneal cavities after the removal of the organs was 2.58 per cent of the body weight. At autopsy, all of the mucous membrane of the intestinal tract was dark red, and there was a great deal of blood in the lumen. The liver was dark and contained much blood. The alterations in the tissues that were observed on microscopic study were marked.

Effects of Hemorrhage and of Direct Transfusion.—Four experiments were performed in which the blood pressure was maintained at a low level for a considerable time by the removal of blood and the introduction of blood by the direct method from a suitable donor. The recipient in all instances was a smaller dog than the donor. Hematocrit readings on the blood of the two animals were approximately the same. No evidence of a reaction as a result of the transfusion was obtained in these experiments. Pain was prevented by the local use of procaine hydrochloride. The average duration of the experiments was seven hours and thirty-four minutes. The blood pressure was lower than normal during the entire time. The average mean arterial pressure remained depressed below 75 mm. for three hours in three of the experiments and one hour in the other. The average time separating the last removal of blood and death was two hours and thirty-one minutes. During this time a good deal of blood was injected. The average quantity of blood that was removed in terms of body weight equaled 4.32 per cent, while the average quantity that was introduced equaled 4.46 per cent. It is to be observed that all of the animals died despite the fact that a slightly greater quantity of blood was injected than was removed. As has been stated, the blood pressure was reduced to a low level by hemorrhage before any blood was injected. There was an increase in the concentration of the red blood cells in all of the experiments. The average quantity of blood remaining in the pleural and

peritoneal cavities after the removal of the organs equaled 2.2 per cent of the body weight. The gross and microscopic alterations in the tissues were marked. The mucous membrane of the intestinal tract was red, and free blood was present in the lumen of the tract. Hemorrhagic areas in the lungs were noted in two animals. In one experiment the wall of the gallbladder was thick and edematous. On microscopic examination, the suprarenal glands showed vacuolation, hemorrhage, capillary congestion, an occasional cell with a necrotic nucleus and polymorphonuclear leukocytes in the cortex. The duodenum showed dilatation and thrombosis of the capillaries and complete necrosis of some of the crypts. Hemorrhage and capillary congestion were present in the heart muscle. The skeletal muscle was essentially normal. The liver showed hemorrhage, congestion and necrosis of liver cells. Capillary congestion and dilatation were noted in the kidneys and lungs. Focal necrosis of lymphoid tissue was present in the spleen. The pancreas showed a moderate amount of capillary congestion.

Effects of Hemorrhage After Ligation of the Bile and Pancreatic Ducts.—With the idea in mind that the bile and pancreatic juice might in the presence of a low blood pressure be responsible for the alterations in the mucous membrane of the intestinal tract, two experiments were performed in which the ducts were doubly ligated and divided. Five days later in one experiment and twelve days later in the other, the blood pressure was reduced to a low level and maintained there as long as possible by the gradual withdrawal of blood. In one experiment, the mucous membrane was slightly less red than that found in the experiments on hemorrhage alone. In the other experiment, the usual amount of reddening was observed. These experiments indicate that the bile and pancreatic juices are not responsible in the main for the changes that were observed. It is realized that there are other juices that pass into the intestinal tract which might exert an effect.

Weights of the Organs in the Various Experiments.—The weights of most of the organs of the body were determined in all of the experiments because it was believed that information as to the location of fluid that escaped from the blood stream could be obtained in this manner. All of the weights are expressed in grams per kilogram of body weight of the animal. The weights of the organs of a group of normal dogs were first determined. The death of most of the animals was produced by electrocution. This method produces a contraction of the spleen, and hence the weights of this organ are probably smaller than they should be. The organs were removed in the same manner in all experiments. The attachment of the organ, including the blood supply, was severed, and the blood that flowed out without pressure on the part was allowed to escape. The material that was present in the lumen

of the intestinal tract was removed before the weight of the tract was determined. There was a great variation in the weights of the individual organs as expressed in grams per kilogram of body weight in the different animals of the same group of experiments. This variation was greater than the difference in the average weights of the organs in the different groups of experiments. No attempt was made to obtain dogs of the same weight and state of bodily nutrition. The differences in the weights of the organs in the various groups of experiments were not great enough or sufficiently constant to allow any conclusions to be drawn as to the distribution of the loss of fluid. In fact, the average weights of the organs except for the intestinal tract and spleen in the control experiments were approximately the same as those obtained in the other studies. The liver was somewhat heavier in the experiments in which histamine was injected. The results of these determinations are given in the table.

COMMENT

Concerning the causes of traumatic shock, Cannon stated,[5] "One of the central problems, if not the most important central problem, of shock is that of discovering the reason for the lowered arterial pressure. The various theories which have been suggested to account for shock are all directed towards the solution of this problem." When hemorrhage occurs from a large blood vessel, a diminution in the circulating volume of blood results. Owing to vasoconstriction, the blood pressure may remain at its normal level. However, if the decrease in the blood volume is too great to be compensated for by vasoconstriction, the blood pressure falls. This mechanism of the production of shock as a result of uncomplicated hemorrhage seems to be generally accepted. On the other hand, there is a good deal of disagreement as to the cause for the decline in the blood pressure following injury to large masses of tissue. It is to be clearly understood that I do not refer to the decline in the blood pressure noted in primary shock or collapse in which the drop in pressure is rapid, is noted immediately following the injury or operative procedure and is usually of short duration. I refer to secondary shock in which the decline in blood pressure occurs usually an hour or more following the injury. A consideration of the various theories which have been offered in an effort to explain secondary shock will not be gone into here. Blalock [1] and Parsons and Phemister [2] showed that there was a loss of a sufficient part of the blood volume into the injured area following trauma to an extremity to account for the decline in blood pressure in animals anesthetized by sodium barbital or ether. It is shown in the present experiments that similar results are

5. Cannon,[4] p. 15.

obtained when trauma is performed in animals in which anesthesia is produced by the injection of procaine hydrochloride into the spinal canal.

It is well known that there are frequently contributing factors, such as cold, insufficient fluids, anesthesia and operation, which further the development of shock. The manner in which ether anesthesia exerts at least part of its ill effects is demonstrated by the present experiments in which ether was administered for long periods. Capillary congestion and hemorrhage were noted in many of the organs. These alterations appeared despite the fact that the blood pressure did not decline greatly. If changes such as these appear in normal anesthetized animals, it is only natural to suppose that similar alterations which are associated with a low blood pressure as a result of uncomplicated hemorrhage or trauma will be accentuated by the administration of ether anesthesia.

As Cannon has stated, the central problem in the study of traumatic shock has to do with the reason for the lowered blood pressure or a determination of the initiating factor. It seems conclusive that the cause of the low blood pressure in experiments of the duration reported here in which large masses of the muscle of dogs are traumatized is due to the loss of red blood cells and of plasma into the local injured area. In other words, the initiating agent in the decline in blood volume and blood pressure is certainly the local loss of part of the blood volume into the tissues at the site of injury. In shock produced by some of the other methods, the explanation is more complicated and is not entirely understood. The shock that is associated at times with abdominal operations in patients is an example of this. Complicating factors include the anesthetic and the fact that the patient is usually already ill. The opening of the peritoneal cavity and the manipulation of the organs may be associated with a decline in pressure which is probably neurogenic in origin. Hemorrhage in varying amounts and many other factors may also form part of the picture.

It has been stated that the loss of fluid into the injured area in the experiments in which an extremity was traumatized was sufficient to cause a marked decline in the blood volume and blood pressure. Having determined this point, I was interested in knowing if there are additional factors that are responsible for the alterations observed at autopsy, following trauma, in the tissues of the body other than those at the site of injury. The method chosen for this study consisted of the removal of blood from unanesthetized dogs in such a manner that the blood pressure was maintained at a low level preceding death for as long as possible. Pain was prevented by the use of local anesthesia in the introduction of cannulas into the vessels. Experiments of this type are relatively free from objections, in that general anesthesia is

not used and other complicating factors are excluded. The arterial blood pressure and pulse pressure were considerably lower than normal throughout the experiments, but death occurred without the blood pressure having remained at a low level for more than an hour or two. Despite this fact, the alterations in the tissues in some instances were rather marked. A low blood pressure of longer duration was obtained in other experiments by a combination of the removal of blood and the introduction of blood in such a manner that death was delayed. The alterations in the tissues were more marked in these studies. The latter experiments are open to criticism possibly on the grounds that the blood that was injected may have been responsible for some of the alterations in the tissues. The fact that changes of a lesser degree occurred in the experiments on hemorrhage alone in which no blood was introduced makes this seem unlikely. In several of the experiments, definite evidences of a reaction as a result of the transfusion appeared, and these studies were discontinued. Since changes in the tissues similar to those reported following death from trauma may be produced by hemorrhage alone, it is apparent that the reduction in the blood volume and blood pressure as a result of the local loss of fluid from the blood stream into the injured area may be solely responsible for all of the alterations in the tissues that are observed at autopsy.

The materials carried to the tissues by the blood may be classed as food, water and oxygen. Of these materials, the one that must be supplied continuously is oxygen. It is probably lack of sufficient oxygen that is directly responsible for the changes in the tissues that appear when the blood volume and blood pressure are greatly reduced. Different tissues vary in their resistance to want of oxygen. The central nervous system and particularly the brain withstand a poor supply of oxygen less well than most of the other tissues of the body. Numerous studies by many investigators have dealt with the effects of the partial deprivation of oxygen on the nervous system, and these studies were not repeated in the present investigation. The most marked alterations in the present studies were usually found in the intestinal tract, the liver and the suprarenal glands. Skeletal muscle was essentially normal. Gesell [6] showed that a diminution in the blood volume does not result in an equal decrease in the blood supply to various tissues of the body. Glandular and muscular tissues probably have their supply diminished most.

The general impression was gained in the present experiments that the degree of alterations in the tissues was dependent in the main on

6. Gesell, R.: Studies on the Submaxillary Gland: IV. A Comparison of the Effects of Hemorrhage and of Tissue Abuse in Relation to Secondary Shock, Am. J. Physiol. **47**:468, 1919.

the length of time that the blood pressure remained at a low level. That there are other factors than this was shown in other experiments. In some of the experiments on hemorrhage, for example, the arterial pressure and pulse pressure were reduced for the entire time, but the pressure was at a low level for only a short while. Apparently a moderate depression of the systolic pressure with a small pulse pressure for a number of hours may result in changes in the tissues. The production of profound anesthesia of long duration by barbital or ether was associated with changes in the tissues. The diminution of the pulse pressure may have been associated with a sufficient decrease in the blood supply to the organs to cause the alterations. It seems more likely that the anesthetics damage the capillaries directly.

In the care of patients, one rarely encounters as a result of hemorrhage a low blood pressure which persists for several hours. If bleeding occurs to the outside from a large blood vessel, usually early death occurs, or the bleeding is controlled, and the blood volume is augmented artificially or by the withdrawal of fluid from the tissues. If a person bleeds to death within a few minutes following injury, it is only natural that the tissues of the body should appear anemic at autopsy. When large masses of tissues such as the muscles of the thigh are injured, the decline in blood pressure is slower, and the duration of the low blood pressure is longer because the speed with which the fluid escapes is retarded by the size of the vessels and the pressure existing in the tissue spaces. After the pressure in the vessels declines, the escape of fluid is further retarded. Since following trauma the blood pressure usually declines slowly and remains at a low level for a considerable time preceding death, the tissues during this period are partially deprived of blood and oxygen, and changes in them take place. Shock following hemorrhage from a large blood vessel is usually associated with a dilution of the red blood cells in the blood vessels, while shock following trauma to tissues is usually associated with a concentration. When bleeding from a large blood vessel occurs, the fluid that is lost is whole blood. If the bleeding is stopped, fluid from the tissue spaces passes into the blood stream, thereby diluting the red blood cells remaining there. On the other hand, the fluid that escapes into the tissue spaces following trauma to masses of tissues consists in the main of blood plasma. The ratio of red blood cells to plasma is much less than that existing in the blood vessels. Fluid that passes from the tissue spaces into the blood stream continues to be lost through the injured capillaries, and an increase in the concentration of the red blood cells results. It has been shown in the present experiments that hemorrhage alone is frequently associated with an increase in the concentration of the red blood cells if the blood pressure is caused to remain at a low level for

an hour or more. This concentration probably occurs because of the loss of fluid through capillaries that are damaged by the decrease in the flow of blood. It was also shown in the present experiments that the transfusion of blood may be entirely ineffective if the blood pressure has been maintained at a low level by hemorrhage alone. Hence it is to be noted that an increase in the concentration of the blood, a lack of favorable response to the transfusion of blood and capillary congestion and hemorrhage are not peculiar to shock due to trauma, as has been supposed, since these findings may be associated with shock due simply to the removal of blood from a large blood vessel.

Freeman [7] recently reported the results of experiments in which it was found that prolonged vasoconstriction of itself results in a loss of blood from the circulation. He stated, "If we examine all factors which are at present known to produce shock or to aggravate the condition if present, we find that they have one physiological action in common. They are all adequate stimuli for producing hyperactivity of the sympathetic nervous system." Even though vasoconstriction is present, it does not follow necessarily that it is the initiating agent in the production of shock. Hemorrhage, for example, is associated with vasoconstriction and a diminution in the blood volume, but the volume of blood is diminished before the vasoconstriction takes place. A low blood pressure of three hours' duration was produced in some of the present experiments by the injection of acetylcholine, which produces vasodilatation. A great increase in the concentration of the red blood cells occurred, and marked alterations in the tissues were observed at autopsy.

Roome, Keith and Phemister [8] found that the loss of relatively small quantities of blood produced death after a decline in blood pressure had been producd by hemorrhage or trauma to an extremity. It was necessary to remove much larger quantities of blood in order to cause death when a similar decline in blood pressure had been produced by hyperventilation, anaphylaxis, administration of histamine, section of the spinal cord and spinal anesthesia. Confirmation of their results was obtained by a different method in the present experiments. The amount of blood that remained in the pleural and peritoneal cavities after the removal of the organs was determined in the various groups of experiments. The average quantity of blood as expressed in percentage of body weight in the different types of experiments was as follows: (1) control, 5.93; (2) ether control, 4.23; (3) barbital control, 5.23; (4)

7. Freeman, H. E.: Decrease in Blood Volume After Prolonged Hyperactivity of the Sympathetic Nervous System, Am. J. Physiol. **103**:185, 1933.

8. Roome, N. W.; Keith, W. S., and Phemister, D. B.: Experimental Shock: The Effect of Bleeding After Reduction of the Blood Pressure by Various Methods, Surg., Gynec. & Obst. **56**:161, 1933.

injection of histamine, 3.56; (5) injection of acetylcholine, 3.46; (6) increased intrapericardial pressure, 4.74; (7) hemorrhage (no replacement and various anesthetics), 1.40, and (8) trauma of the leg (various anesthetics), 1.73. The similarity in the results of the experiments on trauma to an extremity and those on hemorrhage is close.

SUMMARY

The following were some of the findings in the series of experiments reported here:

1. The production of profound anesthesia for an extended time by the administration of sodium barbital or ether was associated with definite alterations in the tissues of the body. In some instances, hemorrhage into the lumen of the intestinal tract occurred. The alterations were slightly more marked with ether than with barbital.

2. The alterations in the tissues that were found following death from hemorrhage using sodium barbital or ether or procaine hydrochloride in the spinal canal as anesthetics were only slightly less marked than those found following death from trauma when the same anesthetics were used. The blood pressure remained at a low level for a longer time in the experiments in which trauma was produced.

3. A comparison of the results of experiments, performed under sodium barbital or ether or spinal anesthesia, in some of which death was caused by hemorrhage and in others by trauma, shows that the quantity of fluid in the injured extremity in the studies in which trauma was produced was approximately equal in amount to the blood withdrawn in the experiments on hemorrhage.

4. The maintenance of the mean arterial blood pressure at approximately 70 mm. for three hours by the injection of acetylcholine or by increasing the intrapericardial pressure was associated with marked alterations in many of the tissues of the body. The mucous membrane of the intestinal tract became red, and hemorrhage into the lumen of the tract occurred.

5. The removal of blood in small amounts at frequent intervals from animals under local anesthesia in such manner that the blood pressure was at a low level for as long a time as possible preceding death was associated with capillary congestion and dilatation in most of the organs and hemorrhage and necrosis of the cells in some of them. Hemorrhage into the lumen of the intestinal tract was observed in most instances.

6. The maintenance of the blood pressure at a low level for several hours prior to death by the combination of the removal of blood and the introduction of blood was associated with marked alterations in the

tissues. The changes appeared to vary directly with the length of time that the blood pressure remained depressed. The animal's own blood was used for the replacement in these experiments, and coagulation was prevented by defibrinating it or by placing it in a solution of sodium citrate or heparin. There was an increase in the concentration of the red blood cells in more than half of the experiments.

7. In other experiments on dogs in which local anesthesia was used, the blood pressure was reduced by hemorrhage, and it was kept at a fairly constant low level for several hours by removing additional blood or by introducing blood by the direct method from a suitable donor. Death occurred in all of the experiments, despite the fact that slightly more blood was introduced than was removed. The gross and microscopic changes in the tissues were marked. Free blood was present in the lumen of the intestinal tract. There was an increase in the concentration of the red blood cells in all of the experiments.

8. The average quantity of blood remaining in the pleural and peritoneal cavities following the removal of the organs was approximately the same in the experiments in which death was produced by hemorrhage and in those in which death was caused by trauma to an extremity. In the other experiments, larger quantities of blood were recovered from the cavities.

Three of the criteria that are frequently given as differential points between hemorrhage and "traumatic shock" are as follows: (1) Hemorrhage is associated with a decrease in the concentration of the red blood cells, while shock is associated with an increase; (2) death following hemorrhage is associated with an anemic appearance of the tissues, while following shock the tissues show hemorrhage and congestion, and (3) the low blood pressure resulting from hemorrhage is promptly recovered from if a transfusion of blood is given, while shock is not greatly benefited by transfusion. The present experiments show that shock which is associated with an increase in the concentration of the red blood cells, with capillary congestion and hemorrhage in the tissues and with a negative response to the transfusion of blood, can be produced by hemorrhage alone. A prolonged low blood pressure as a result of hemorrhage from a large blood vessel is rarely encountered in patients, because early death or control of the bleeding, with or without the introduction of fluids, usually takes place. On the other hand, one frequently encounters a prolonged low blood pressure which results from trauma to tissues. In this condition, the injury to many small blood vessels allows the escape of red blood cells and of plasma. The loss of fluid and hence the decline in blood pressure are slower than in hemorrhage from a large blood vessel because of the smaller size of the vessels and the greater pressure in the tissues where

the fluid escapes. The results of the treatment of shock due to the loss of blood from a large blood vessel and that due to the loss of fluid from many small vessels in an injured area are different in the early stages in that if the bleeding from the large vessel is stopped, blood introduced into the blood stream will stay there, whereas it is impossible to control entirely the loss of fluid from the many small vessels. If, however, a low blood pressure which persists for several hours results from either of these types of injury, the condition of affairs is more nearly the same in that general injury to the capillaries takes place as a result of the insufficient flow of blood, and fluid introduced into the blood stream will not be retained.

It is to be emphasized that this study is not concerned with a rapid decline in the blood pressure such as that produced by vigorous manipulation of the abdominal organs, by spinal anesthesia or by injury to the central nervous system. Neither is it concerned with postoperative shock, which may be caused by a combination of many factors, such as the disease that prompted the operation, hemorrhage, infection, anesthesia, loss of fluid from the exposed surfaces and dilatation of large areas of capillaries. It is concerned primarily with the decline in blood pressure which is slow in onset and progressive and which was produced in most of these experiments by the slow withdrawal of blood and by trauma to large masses of muscle.

THERAPEUTIC USE OF CONCENTRATED ANTISTREPTOCOCCUS SERUM OF NEW YORK STATE DEPARTMENT OF HEALTH

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EARLY INVESTIGATIONS OF STREPTOCOCOUS SERUM

The serum of animals immunized against hemolytic streptococci was early introduced for the treatment of human disease. Marmorek[1] employed a streptococcus of high virulence to immunize horses, asses and sheep. The serum of these animals was then found to possess preventive and curative value in the streptococcic infection of rabbits. Marmorek treated forty-six patients with severe erysipelas by the injection of from 5 to 20 cc. of serum, and all but one made a rapid recovery. He believed that a potent serum could be obtained only by employing for immunization a virulent and toxic strain of the streptococcus.

Subsequent clinical experience with serum therapy in streptococcic infections has resulted in conflicting opinions. Some reports were favorable, but perhaps more were unfavorable. In part, these discrepancies may be ascribed to the use of different serums, but this explanation is not quite adequate. Even today we are unable to explain in a wholly satisfactory manner the variable clinical results.

In some diseases the natural course of the malady, when uninfluenced by therapeutic meddling, tends to follow a more or less definite schedule and to terminate in recovery or in death. In other disorders, the course tends to be variable, and the complications and eventual outcome are lacking in uniformity. Infections with the hemolytic streptococci belong in the latter category. On that account the appraisal of any therapeutic agent for streptococcic infections is made difficult, and any decisive statement in regard to this matter is calculated to promote controversy rather than conviction.

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1. Marmorek, A.: Le sérum antistreptococcique, Compt. rend. Soc. de biol. **47**:230, 1895; Ann. Inst. Pasteur **9**:593 (July 25) 1895.

The preparation of the serum presents difficulties, and the various samples on the market are evidently far from uniform in potency. The methods for testing potency are somewhat unsatisfactory, and the results of titration tests are, as a rule, less definite and less reliable than in the case of such therapeutic serum as that of diphtheria or of tetanus. Apparently much of the streptococcus serum furnished for therapeutic use is comparatively feeble in action.

It is also possible that differences in variety among the hemolytic streptococci may be of significance in this connection. A serum effective against one particular strain may conceivably be without effect on another strain. As early as 1897, Van der Velde [2] employed for immunization of animals a number of streptococcus cultures isolated from various clinical types of streptococcic infection in man, hoping in this way to produce a more effective polyvalent therapeutic serum. It will be noted that this idea is somewhat different from that of Marmorek, who relied on one strain and placed emphasis on high virulence and high toxicity of the culture strain employed. The question is still somewhat controversial. However, the desired improvement in clinical results was not realized, and in the early part of this century serum therapy in streptococcic infections fell into disuse.

RENEWED INTEREST IN SERUM THERAPY OF STREPTOCOCCIC INFECTIONS

A reawakened interest in antistreptococcus serum gradually gathered momentum as a result of studies on scarlet fever, particularly because of the promise of practical therapeutic results by the use of serum in this disease. Pioneer work in this field was carried out by Moser [3] and by Savchenko,[4] but this work received little or no attention in the United States until George F. Dick [5] and Gladys Henry Dick presented the

2. Van der Velde, H.: De la nécessité d'un sérum antistreptococcique polyvalent pour combattre les streptococcies chez le lapin, Arch. de méd. expér. et d'anat. path., Paris **9**:835, 1897.

3. Moser, P.: Ueber die Behandlung des Scharlachs mit einem Scharlachstreptokokkenserum, Wien. klin. Wchnschr. **15**:1053, 1902; Ueber antistreptokokken serum bei Scharlach, Berl. klin. Wchnschr. **40**:13, 1903.

4. Savchenko, I. G.: Opregoloolenii protivoskarlalinnoi sivorotki (Preparation of Antiscarlatinal Serum), Russk. vrach **4**:797, 1905.

5. Dick, G. F., and Dick, Gladys H.: Experimental Inoculations in Scarlet Fever, J. A. M. A. **77**:782 (Sept. 3) 1921; Experimental Scarlet Fever, ibid. **81**:1166 (Oct. 6) 1923; A Skin Test for Susceptibility to Scarlet Fever, ibid. **82**:265 (Jan. 26) 1924; The Etiology of Scarlet Fever, ibid. **82**:301 (Jan. 26) 1924; Scarlet Fever Toxin in Preventive Immunization, ibid. **82**:544 (Feb. 16) 1924; Scarlet Fever Antitoxin, ibid. **82**:1246 (April 19) 1924; Prevention of Scarlet Fever, ibid. **83**:84 (July 12) 1924; Scarlet Fever, Am. J. Pub. Health **14**:1022, 1924.

results of their investigations. These authors appear to have induced scarlet fever by the inoculation of pure cultures of streptococci into the throats of volunteer human subjects. They have been able to obtain a toxic filtrate of broth cultures which they employ by injection into the skin as a test for susceptibility to scarlet fever. With an amount equal to 1,000 skin test doses of toxic filtrate they were able to cause transient symptoms of mild scarlet fever in susceptible adults. They also produced a concentrated immune horse serum and found that an amount of this antitoxic (immune) horse serum sufficient to neutralize 20,000 skin test doses of toxin constitutes an effective therapeutic dose for scarlet fever. In a satisfactory serum the volume of this therapeutic dose does not exceed 20 cc. Given early, in adequate dosage, they found that it shortens the course of scarlet fever and reduces the number of complications and sequelae. When injected into the skin of a patient in the florid stage of scarlet fever, this serum is able to bring about a blanching of the cutaneous erythema which is apparently similar in all respects to the blanching obtained by the analogous use of serum from a person recently convalescent from scarlet fever. This phenomenon furnished a clearly recognizable proof of some protective property in the serum.

These observations served to encourage the renewal of efforts to produce antistreptococcus serum, and attempts to extend the field of therapeutic application to other diseases than scarlet fever followed as a matter of course. Erysipelas may be particularly mentioned. Clinical experience has not been uniformly favorable in the serum therapy of either scarlet fever or erysipelas, but the favorable reports have been sufficiently numerous to encourage the continued production of serum for the treatment of these conditions.

However, even as late as 1923, there were commanding voices raised against the use of antistreptococcus serum. Thus Gay,[6] in July 1923, was able to say: "There is nothing approaching acceptable evidence of the successful treatment by serum of any of the streptococcal infections, except possibly in the complications of scarlet fever. Many definite reports of failure to procure results are available." It should be noted, however, that this author seems to have modified somewhat his position on this question in recent years. In 1930, he[7] reported that experimental streptococcic pleurisy of rabbits could be prevented in about 20 per cent of the cases by the use of a potent antistreptococcus serum, and that such a serum combined with exudate cells afforded a high degree of protection.

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6. Gay, F. P.: The Use of Antiserums in the Treatment of Diseases, J. A. M. A. **81**:284 (July 28) 1923.

7. Gay, F. P.: The Grades of Resistance and Immunity to Bacteria, Tr. A. Am. Physicians **45**:321, 1930.

SERUM THERAPY IN STREPTOCOCCIC BACTEREMIAS

In France, a renewed interest in antistreptoccus serum seems to have been initiated by Vincent [8] in 1929. Successful treatment of streptococcic bacteremia by the use of Vincent's serum has been reported by several authors [9] since 1929. The dosage of his serum is 100 cc. per day; the administration is started as soon as the diagnosis can be made, and the amount is diminished only as the infection recedes. According to Vincent, serotherapy should be continued until all symptoms have disappeared and for two or three days after complete cessation of fever.

In England, Benson [10] and Rankin observed one hundred and fourteen cases of puerperal sepsis, all with hemolytic streptococci demonstrated by blood culture. The puerperal antistreptococcus serum of Burroughs, Wellcome and Company was given to 20 patients, and the concentrated scarlatinal streptococcus antitoxin of the same company was administered to 37 patients. The total dosage varied from 100 to 330 cc. The mortality in the group treated with serum was 75 per cent, and in the control group of fifty-seven patients without serum treatment the mortality was 68 per cent. Serum reactions were quite distressing, especially after intravenous administration. These observations do not favor the use of antistreptococcus serum.

Penfold [11] and Corkill, in Australia, observed steady improvement and eventual recovery in a patient with streptococcic septicemia treated with serum. These authors recommend that white mice be inoculated with the blood culture from the patient and then be given injections of each available kind of antistreptococcus serum. Death of the control mice and survival of the mice treated with serum serve to indicate a specific therapeutic value of the particular serum. In this way one may select the best available serum for the particular patient.

In the United States, recent experience seems to have been more favorable to serum therapy in streptococcic infection. J. H. Park Jr.[12]

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8. Vincent, H.: Sur les résultats thérapeutiques donnés par un nouveau sérum antistreptococcique, Compt. rend. Acad. d. sc. **188**:1348 (May 27) 1929.

9. Hubert, C.; Girard, L., and Hemon: Deux cas de septicémie à streptocoques guéris par le sérum antistreptococcique de Vincent, Bull. Acad. de méd., Paris **104**:405 (Nov. 25) 1930. Vincent, H.: La septicémie à streptocoques. Son traitement par un nouveau sérum antistreptococcique, ibid. **105**:735 (May 5) 1931. Courty, M. L.: Septicémie à streptocoque traitée et guérie par le sérum de Vincent, ibid. **106**:89 (July) 1931. Canuyt, G.: Streptococcus Septicemia of Pharyngeal Origin; Cure Following Therapy by Fixation Abscess and Vincent's Antiserum, Strasbourg méd. **92**:560 (Sept. 15) 1932.

10. Benson, W. T., and Rankin, A. L. K.: Treatment of Puerperal Septicemia with Antitoxic Serum, Lancet **1**:848 (April 22) 1933.

11. Penfold, W. J., and Corkill, O. B.: Septicemia with Recovery, M. J. Australia **1**:341 (March 17) 1928.

12. Park, J. H., Jr.: The Serum Treatment of Acute Streptococcic Infection of the Respiratory Tract of Infants and Children, M. Rec. & Ann. **24**:581, 1930.

treated forty-one children with acute streptococcic infection of the respiratory tract by injecting polyvalent antistreptococcus serum together with therapeutic scarlet fever antitoxin. When this treatment was administered before the fifth day it was followed by complete recovery without sequelae in every case. These results presented a marked contrast when compared with those in the other children afflicted in the same outbreak who did not receive the serum.

Jopson [13] and Eiman observed forty-three cases of infection of the blood stream with hemolytic streptococci. In twenty no serum was given and in four the injections were either inadequate or administered too late, making a total of twenty-four cases with nineteen deaths and five recoveries. The survivors had (1) mastoiditis with sinus thrombosis and high fever for forty days; (2) high fever for five days following mastoidectomy, (3) abortion with high fever for thirty days and (4) cellulitis of the hand treated by incision and drainage (two cases). Nineteen of the patients received antistreptococcus serum in total amounts between 150 and 750 cc. Of these, fifteen recovered and four died. The four fatalities were due to (1) abortion with multiple abscesses in the myometrium and thrombosis of the ovarian and renal veins, (2) cellulitis of the leg, (3) abortion with clinical peritonitis (no necropsy) and (4) abortion and ruptured uterus with generalized peritonitis (necropsy). The authors distinguish between the shower type of septicemia and massive invasion of the blood stream. They also discuss the significance of other factors, such as the state of the various organs, maintenance of water balance, nutrition, the proper use of transfusions and the surgical treatment of primary and secondary foci. Hypersensitiveness to horse serum could not always be overcome even after seven or more carefully graded doses of the serum, and on that account these authors occasionally employed bovine serum. They regard the streptococcus serum as of decided value.

POLYVALENT SERUM PROBABLY UNNECESSARY

Amoss, Persons and Hansen-Prüss [14] treated five patients with antistreptococcus serum, all of whom were critically ill with streptococcic pneumonia and not expected to live. The serum was that of the New York State Board of Health and a commercial brand. Both seemed to produce beneficial results. All five patients recovered, and all suffered from serum sickness. These authors also demonstrated the protective effect of the serums on mice.

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13. Jopson, J. H., and Eiman, J.: The Serum Treatment of Bacteremia Due to Hemolytic Streptococcus, Ann. Surg. **92**:910 (Nov.) 1930.

14. Amoss, H. L.; Persons, E. L., and Hansen-Prüss, O. C.: Serum in the Treatment of Streptococcus Pneumonia, Tr. A. Am. Physicians **46**:208, 1931.

In discussing this paper, Wadsworth stated that a serum produced by immunizing horses with the Dochez streptococcus strain N.Y. 5 had been found to protect against between 75 and 80 per cent of five hundred strains of streptococci tested.

In some of his later publications, Wadsworth[15] questioned the recognition of a specific streptococcus of scarlet fever. The serum produced by immunizing a horse with the Dochez strain N.Y. 5 from a case of scarlet fever was found to neutralize the toxins of 65 per cent of pathogenic streptococci, regardless of their origin. The serum of an animal immunized by the use of streptococcus from erysipelas gave analogous results. Wadsworth does not regard the toxins of these different bacterial strains as identical, and he recognizes differences in the serums. However, he considers scarlet fever not as a specific infectious disease but rather as a manifestation of streptococcic infection which is in varying degree characteristic.

Comparative tests in the laboratory of the New York State Department of Health during a period of five years have shown that relatively few samples of streptococcus serum possess a potency as high as 400 units per cubic centimeter. Only when the Dochez streptococcus strain N.Y. 5 has been employed has it been possible to get a horse serum with a potency of from 600 to 800 units per cubic centimeter. Most of the samples of streptococcus serum in general use continue to approximate only minimum standards of potency.

Wadsworth expressed the belief that the interaction between streptococci and the body defenses is of a complex nature, such that various clinical manifestations appear as a result of infection of different hosts with the same identical strain of streptococcus. Furthermore, the influence of the therapeutic serum is also complex and not well understood. Evidently its effect is influenced by other defense mechanisms of the animal host which themselves are still obscure. He concludes that streptococcus serum has a demonstrated value in the treatment of scarlet fever, erysipelas and streptococcic sore throat and an apparent but not clearly proved value in more severe streptococcic infections, even those with bacteremia. He expects further light to be shed on the subject of streptococcus serum therapy as a result of clinical experience with a newer concentrated serum of high potency that titrates approximately 3,000 units per cubic centimeter. This serum has recently been produced in his laboratory at Albany.

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15. Wadsworth, A. B.: Studies of the Streptococci and Anti-Streptococcus Serum in Scarlet Fever, Compt. rend.-Congr. Internat. de microbiol. **1**:308, 1931; Serum Therapy: Its Value in Pneumonia, Meningitis, Scarlet Fever and Other Streptococcus Infections, J. A. M. A. **99**:204 (July 16) 1932; Recent Advances in the Serum Therapy of Pneumonia, Meningitis, Scarlet Fever and Other Streptococcus Infections, Tr. A. Am. Physicians **47**:161, 1932; Serum Therapy of Streptococcus Infection, Canad. Pub. Health J. **24**:1 (Jan.) 1933.

THE CONCENTRATED SERUM OF THE NEW YORK STATE DEPARTMENT OF HEALTH

Late in 1931, Dr. Augustus B. Wadsworth, director of the division of Laboratories and Research, New York State Department of Health, made available to us, with certain restrictions as to its use, an almost unlimited supply of the newer, high titer, concentrated serum, with a potency of from 2,500 to 3,000 units per cubic centimeter.

According to information received from Dr. Wadsworth, the serum is obtained by immunization of horses, first with living streptococci of the Dochez [16] strain N.Y. 5 injected into a mass of agar previously introduced in a fluid state under the skin of the animal and allowed to harden there (Dochez agar-culture method). Later, subcutaneous doses of toxic filtrate, supplemented by further injections of living organisms by the agar-culture method, are given. The treatment of the horses is continued for from one to two years or even longer. Eventually the serum of the horse has a potency of from 800 to 900 units per cubic centimeter. Concentration is accomplished by precipitation with ammonium sulphate and further purification by iso-electric precipitation of the water-insoluble globulin, giving a final potency of from 3,000 to 3,600 units per cubic centimeter.

The opportunity to test this serum in serious streptococcic infections was welcomed by us because we were occasionally placed in a somewhat difficult position when asked to help in the treatment of septic patients. Subsequent to a certain measure of success attained in the bacteriophage [17] treatment of bacteremias due to staphylococci and to colon bacilli, some of our clinical colleagues appealed to us for assistance when they were confronted with cases of septic infection, regardless of the specific nature of the infecting microbe. Not infrequently the important infectious agent would prove to be the hemolytic streptococcus, an organism against which we did not possess any potent bac-

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16. Stevens, F. A., and Dochez, A. R.: The Study of Hemolytic Streptococci Associated with Scarlet Fever, Proc. Soc. Exper. Biol. & Med. **21**:39, 1923. Dochez, A. R., and Sherman, L.: Significance of Streptococcus Hemolyticus in Scarlet Fever: Preparation of a Specific Antiscarlatinal Serum by Immunization of Horse to Streptococcus Hemolyticus-Scarlatinae, J. A. M. A. **82**:542 (Feb. 16) 1924; Studies Concerning the Significance of Streptococcus Haemolyticus in Scarlet Fever, Proc. Soc. Exper. Biol. & Med. **21**:184, 1924. Dochez, A. R., and Stevens, F. A.: Studies on Biology of Streptococcus: Agglutination and Absorption of Agglutinins with Streptococcus Scarlatinae, J. Exper. Med. **40**:253, 1924; Studies on Biology of Streptococcus; Occurrence of Streptococcus Scarlatinae in Convalescence and in Complications of Scarlet Fever, ibid. **40**:493, 1924.

17. MacNeal, W. J., and Frisbee, F. C.: Bacteriophage as a Therapeutic Agent in Staphylococcus Bacteremia, J. A. M. A. **99**:1150 (Oct. 1) 1932. MacNeal, W. J.; Frisbee, F. C., and Applebaum, Martha: III. Use of Bacteriophages in the Treatment of Colon Bacillus Septicemia, Arch. Surg., to be published.

teriophage. It became a source of satisfaction for us to have available a streptococcus serum for use in such patients. At first the invitation to employ bacteriotherapeutic measures came only after the condition of the patient appeared to be quite hopeless. Later it became possible for us sometimes to use the serum even in patients who seemed to have a good chance to survive without it. More recently it has been possible to use the serum in still earlier stages of streptococcic infection in order to forestall threatened extension of the infection and consequent mutilating operative procedures.

The case histories to be presented in the succeeding papers of this series have not been selected with the purpose of proving any thesis. They represent our total experience in the use of the concentrated streptococcus serum of the state laboratory during a period of approximately two years. It is not certain that the most effective methods of employing serum therapy in streptococcic infections have yet been ascertained. We are convinced, however, that the serum is being more intelligently and more effectively employed in our more recent cases than in the earlier ones of our series. We are also certain that the serum therapy of streptococcic infections is now held in much higher esteem by our clinical associates than it was in 1931.

SUMMARY AND CONCLUSIONS

1. Serum therapy of streptococcic infections has been a controversial subject almost since the description of the first streptococcus serum by Marmorek in 1895.

2. After a period of disfavor and disuse, interest in streptococcus serum was revived by its somewhat successful application in the treatment of scarlet fever and of erysipelas.

3. While the classification of the hemolytic streptococci is still confused, there is no valid reason for distinguishing between therapeutic serums for different clinical types of streptococcic infection.

4. The most potent antistreptococcus serum now available appears to be the concentrated serum of the laboratory of the New York State Department of Health.

A REVIEW OF UROLOGIC SURGERY

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(Concluded from page 696)

BLADDER

Tumors Among Dye Workers.—Anderson [24] stated that occupation is a causal factor in the development of vesical tumors among workers in aniline dyes. The duration of occupation and not the age of the patient is the determining factor in the development of such tumors. The familial history is apparently an unimportant factor. Neither positive nor negative symptoms and signs are conclusive evidence of the presence or absence of vesical tumors among these persons. A positive diagnosis of such a tumor can be made only by early and periodic cystoscopic examinations.

Gehrmann [25] stated that vesical tumors occur more commonly among dye workers than in other persons and that in his experience such tumors occurred among 4.5 per cent of the former. The combined experiences of the dyeing industries of Germany, Switzerland, England and America indicate that aniline, alpha and beta naphthylamine and benzidine probably are the etiologic compounds. Vesical tumors may appear at any time after two years' exposure, and removal of the worker from the dye operation does not eliminate the possibility of the future development of the growth. The adoption of a completely closed and properly ventilated process, together with careful medical supervision

24. Anderson, L. W.: Incidence, Symptoms and Signs, Results of Survey, J. Urol. **31**:148 (Feb.) 1934.

25. Gehrmann, G. H.: The Carcinogenetic Agent-Chemistry and Industrial Aspects, J. Urol. **31**:126 (Feb.) 1934.

and protection will eliminate the hazard, but these methods will require many years of active enforcement and must continue so long as the compounds are made.

Gay [26] stated that the pathologic characteristics of tumors of the bladder among dye workers are not essentially different from those of tumors of unknown origin. The tumors are single or multiple, papillary or sessile, infiltrating or noninfiltrating, ulcerating or nonulcerating; there may also be any combination or sequence of these characteristics. An analysis of 124 of the approximately 200 cases reported from various German sources indicates that the incidence of carcinoma is about twice that of papilloma. The occurrence of nonepithelial neoplasms is rare. In the cases reported papillomas are more often single, and carcinomas are more often multiple. Thirty-seven tumors were situated on the trigon, and 16 were found elsewhere in the bladder. In this series tumors situated elsewhere than on the trigon appeared to be more malignant than those situated at the base of the bladder. Although the tumor may invade the tissues of the pelvic cavity, metastasis is extremely rare. There are many records of submucous hemorrhages, localized areas of hyperemia or cystitis in which tumors developed later.

Gay gave data on 17 tumors of the bladder occurring among dye workers, which had been examined microscopically. Seven were papillomas of grade 1. The remaining 10 lesions were classified as follows: 4, papillary carcinoma of grade 2; 1, carcinoma of grade 3; 1, carcinoma of grade 4; 3, coexistent papilloma and carcinoma; 1 was diagnosed as carcinoma but not graded. The multiple tumors were all carcinomas. Seven of the single tumors were papillomas, and 3 were carcinomas. In 8 cases the tumors were not preceded by symptoms.

Washburn [27] reported that 23 men, all engaged in the manufacture of dyestuffs in the United States, had been treated for tumor of the urinary bladder. Eleven of these men had single tumors which were treated through the cystoscope by fulguration with the bipolar current, and 7 had multiple tumors which were treated in the same manner. Two patients in this group have had new lesions in a different situation. Open operation was performed in 5 cases; 2 patients of this group had a single tumor, graded 3 and 4, respectively. The remaining 3 lesions were multiple; 2 were graded 3 or 4, and 1 was clinically malignant but unfavorable for biopsy. There have been no deaths in the series.

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26. Gay, D. M.: Pathology of Anilin Tumors of the Bladder, J. Urol. **31**: 137 (Feb.) 1934.

27. Washburn, V. D.: Treatment of Anilin Tumors of the Urinary Bladder, J. Urol. **31**:155 (Feb.) 1934.

Tumors.—Kretschmer [28] and other members of the Committee on Carcinoma Registry reviewed reports of 902 cases of epithelial tumor of the bladder submitted to the Carcinoma Registry of the American Urological Association. The sex incidence in this series is approximately 76 per cent males and 23 per cent females. The peak age incidence was from 55 to 59 years; 62 per cent of the patients were between the ages of 50 and 69 years. Sixteen epithelial tumors of the bladder occurred among aniline dye workers. A family history of carcinoma was of no apparent significance in this series of cases of carcinoma of the bladder.

Tumors involving the lateral walls, trigon and neck of the bladder constituted 76.6 per cent of all the tumors in this series. Less than half of the neoplasms in these situations were highly malignant, whereas 3 of every 4 tumors of the vault of the bladder were of grades 3 or 4. The site of the growth has little apparent relation to the prognosis except when the vault is involved, in which case the prognosis for five year cures is 18.7 per cent.

Of the total number of epithelial tumors, 643 were single and 250 were multiple. Only 1 of every 3 multiple tumors was highly malignant, whereas half of the single tumors were of grades 3 or 4. Forty-five per cent of the tumors in this series were larger than 5 cm. in diameter when first observed. When the tumor was less than 2 cm. in diameter the results were greatly improved. Metastasis was present in approximately 10 per cent of the cases in this series.

Recurrence followed treatment in 46.2 per cent of the cases. Detailed observations were made at necropsy in 79 of the 902 cases. On microscopic examination approximately half of the tumors were found to be infiltrating. In 5 per cent of the cases tumors of more than one type were found. Hematuria was the initial symptom in 63 per cent of the cases, and it was discovered on examination in 76 per cent of the cases. Only 10.8 per cent of the patients were completely examined and the diagnosis established within one month. In 48 per cent of the cases in the series the diagnosis was delayed more than one year. Loss of weight constituted a major complaint in slightly more than one fourth of the cases.

Careful preoperative preparation of patients with carcinoma of the bladder should be observed as a means of reducing the operative mortality. More than one third of the patients were found to have serious impairment of renal function. Cytoscopic examination, biopsy and

28. Kretschmer, H. L.; Barringer, B. S.; Braasch, W. F.; Dean, A. L.; Ferguson, R. S.; Keyes, E. L., and Smith, G. G.: Cancer of the Bladder; a Study Based on 902 Epithelial Tumors of the Bladder in the Carcinoma Registry of the American Urological Association, J. Urol. **31**:423 (April) 1934.

roentgen examination are the principal means of diagnosis, and they were shown to be highly accurate in this series. The standard methods of treatment were resection, fulguration and irradiation. Of 349 patients observed for five years or more, 33.24 per cent were alive at the end of that period.

Keyes [29] presented a report on case histories, the basis of which constituted a continuation of the histories of 31 patients with vesical tumor treated by suprapubic implantation of metal capsules containing radium. These 31 cases have been reported previously and the method of operation described. They are the first 31 cases in which operation was performed by Keyes' method. The operations were performed between December 1925 and March 1928. The results five years after these operations are quite gratifying in spite of the fact that 4 cases have been included (4, 15, 16 and 17) in which initial treatments were made by resection or by implantation of radium using less satisfactory methods; 2 with glass seeds and 2 with steel needles containing radium element. The 4 patients have died of carcinoma. In the previous report 2 deaths from operation were recorded; 1, three days after suprapubic implantation of radium; the other, caused by ileus, following resection of the bladder for persistent tumor of the vault after repeated implantation of radium had failed. In the previous report results were tabulated after dividing the types of papillomas into four groups: grades 1, 2, 3 and 4.

Keyes stated that it is interesting to compare the prognostic accuracy of the older methods of more or less combined clinical and pathologic malignancy with the modern grading. According to the older classification 8 tumors were graded 1 and 2. Only 1 (12.5 per cent) of these patients died. Eleven tumors were of grade 3; 2 patients died following operation, and 3 died later of carcinoma, making a mortality of nearly 50 per cent. One of these patients lived three and a half years from the time of the original treatment. Thirteen of the 14 patients died of carcinoma clinically graded 4.

Keyes commented that all epithelial tumors of the bladder graded 1 or 2 should be regarded as curable and treated by fulguration, implantation of radon or cystectomy unless the patients were moribund or unless for other reasons operation could not be performed. For lesions of grade 3 the prognosis is poor. He reported that only 23 per cent of such lesions were controlled for five years. Most of the deaths from carcinoma occur in the first two years. The prognosis for lesions of grade 4 is even worse. One patient had remained at work and apparently was well for six years, when he suddenly died of carcinoma.

29. Keyes, E. L.: Five-Year Results of Suprapubic Radium Implantation into Bladder Tumors, Tr. Am. A. Genito-Urin. Surgeons **26**:207, 1933.

Keyes reported 37 implantations of radon with but 1 postoperative death. Postoperative spasms which follow implantation of glass seeds do not occur unless more than twenty radon seeds are implanted. Twenty-seven of the operations were followed by no more discomfort than is to be expected after cystotomy. The 6 patients who required more than one operation submitted to the second operation without comment. Resection is not applicable to tumors about the trigon or vesical neck, although tumors in these sites present no peculiar difficulties to the implantation of radon. Ureteral reimplantation does not have to be considered. The operative mortality is much lower, and the stay in the hospital is so much shorter that it pays for the radium. In this series drainage was carried out in 11 cases, and in the 26 cases in which suture was made without drainage, wounds broke open in 11. In the 15 cases in which leakage did not occur, the average postoperative stay of the patients in the hospital was fifteen days; in the other cases the postoperative fistula remained open on the average for twenty-three days. Keyes stated that it is to be hoped that the permanency of cure with radium is no longer questioned.

Ferguson [30] stated that it had been his privilege to study annually the registry of vesical tumors and to report the contents of it to the American Urological Association. Last year he found 600 cases in the registry, in 154 of which treatment had been given more than five years previously. The figures for five year survivals for each grade at that time corresponded closely to those reported by Keyes, being 72 per cent for grade 1, 43 per cent for grade 2, 24 per cent for grade 3 and 4 per cent for grade 4. This year there are reports in the registry of more than 600 tumors, and the comment that the rate of growth of this registry to date has exceeded the rate of growth of any other registry of national scope is interesting.

Graves and Militzer [31] stated that metastasis to bones from carcinoma of the bladder is more common than is generally supposed. Metastasis may be of slight extent or widespread. Aside from the pelvis there seems to be no particular predilection for any bones. A search for evidence of metastasis must, therefore, be thorough. One case of carcinoma of the bladder with metastasis to the lungs, liver and right fourth rib, histologically proved, is presented. In addition, 4 cases of carcinoma of the bladder with roentgenologic evidence of metastasis to bone are reported. Osseous metastasis from carcinoma of the bladder is usually of the osteoclastic type, although some cases of carcinoma of the bladder also show osteoplastic changes. Two cases

30. Ferguson, Russell, in discussion of Keyes,[29] p. 227.

31. Graves, R. C., and Militzer, R. E.: Bone Metastases from Carcinoma of the Urinary Bladder, Tr. Am. A. Genito-Urin. Surgeons **26**:185, 1933.

of carcinoma of the bladder revealing changes in bone suggestive of Paget's disease are reported. Great caution must be observed in condemning a case as inoperable because of associated lesions in the bone.

Nicholls [32] stated that papillomas of the bladder do not tend to metastasize, and if extension does take place it is usually by direct spread to the pelvic tissues or by lymphatic structures to the preaortic glands. Discontinuous metastasis of a benign vesical papilloma is extremely rare, and the widespread skeletal deposits so common in prostatic carcinoma are almost unknown in vesical malignancy.

Nicholls reported a case of apparently benign, transitional cell papilloma of the bladder with multiple skeletal tumors of the same type of growth. The vesical tumor, which on section proved to be a benign papilloma, had been excised by cautery. Three years later the patient returned because of pain and swelling in the right knee. Some hematuria had occurred in the interval and on the posterior wall of the bladder there was a recurrence of the villous tumor, which was removed suprapubically. Ten days later roentgenograms revealed destruction and calcification of the right femur and tibia. Following arthrotomy for biopsy, the tumor of the knee increased, and a mass appeared in the right iliac fossa. The patient died one month after cystotomy had been performed. Extensive metastasis of a transitional cell papilloma similar to the one in the bladder was found in the lungs, ribs, pelvis, right femur and tibia. Sections of all these tumors revealed regular papillary processes in each case, with cells regular in shape and size and no mitosis. Ossification was present in the sections taken from the bony tumors. Section of the vesical wall in the region of the removed tumor gave no evidence of neoplasm.

This case is singular in that the vesical tumor was benign both clinically and microscopically. A tumor removed three years later was single and noninfiltrating, and extensions could not be found in the vesical wall at postmortem examination. The bony deposits were likewise microscopically not carcinomatous, although their growth was rapid and destructive.

Nicholls speculated as to the mode of entry of these cells into the blood stream and concluded from the clinical history that it was independent of either operation. He compared the picture to the multiple thyroid metastasis seen in malignant adenoma of the thyroid gland, which may erode blood vessels and give rise to distant metastasis early in its career when it is small and confined to its capsule, and thus clinically benign.

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32. Nicholls, M. F.: A Case of Vesical Papilloma with Widespread Metastases, Brit. J. Surg. **21**:108 (July) 1933.

Stones.—Adrian [33] reported the remarkable case of a woman aged 50 in whom calculi had taken an extraordinary course from the gall-bladder to the urinary bladder and had been expelled through the urethra. Only 7 similar cases, all occurring between the years 1836 and 1897, have been reported in the literature. Six of these patients were women, and the sex of the seventh was not indicated. The case reviewed by Adrian was first observed in 1919, and the patient has never been lost sight of since. For nine months the patient had expelled through the urethra at least one hundred stones composed of pure cholesterol, forty-eight of which she had saved and turned over to Adrian for study. The stones were of different sizes and shapes, but all were characterized by extreme lightness of weight; these forty-eight stones, which nearly filled a wine glass, weighed altogether only 21 Gm. and floated when placed in water. Most of them were gray, smooth and shiny, with faceted surfaces. However, on one occasion, a stone of an entirely different appearance, yet of the same chemical character, arrived in the urethra; after several days of intermittent urinary retention, culminating in complete retention for sixteen hours, the stone was removed at operation. Cystoscopy revealed a brown rounded calculus, approximately the size of a walnut, with a corrugated surface without facets, lying in a rather unusual position in the left side of the bladder, attributed by Adrian to deformation of the floor of the bladder. In the course of extraction the stone unfortunately was broken to some extent, leaving, however, one large fragment and several small ones that could be patched together; reconstruction of the stone showed that it had been cone-shaped, about 13 mm. in diameter at its base and 12 mm. in height; its weight was 35 Gm. Because of bleeding, cystoscopy could not be carried out for a week; when it was carried out, however, it revealed an empty bladder, the mucosa of which showed no signs of acute inflammation. The ureteral orifices appeared like large slits in the middle of numerous prominences of the hypertrophied vesical musculature. In the supero-anterior part of the cavity, above the "air-bubble," in the middle, Adrian discovered a diverticulum the size of a large almond (about 1 cm.) with its greater diameter running horizontally. Its margins were irregular, and it appeared to be empty.

From that time on the patient never had any further vesical trouble, and her restoration to health caused her to refuse cystography, which might have revealed the exact site of the diverticulum. She did, however, consent to insufflation of the colon, which revealed that the entire transverse colon passed in front of the liver, which was strikingly ptosed. The chemical analysis of the stones showed them to be typical biliary calculi.

33. Adrian, Charles: Calculs biliaires dans la vessie d'une femme, Bull. Soc. franç. d'urol. **37**:386 (Dec. 18) 1933.

Despite ptosis of the liver, it is impossible to assume the existence of a direct communication between the gallbladder and the urinary bladder as the result of simple inflammatory adhesions of the walls of the two organs. Such a communication, if it ever took place, was the result of the interposition of a more or less latent focus of peritonitis. But there is another passage that the calculi may have made use of to reach the bladder, namely, the urachus, after the establishment of an adhesion between the gallbladder and a persistently patent urachus. Among the seven cases found in the literature, two were of this kind (Koestlin, Kroenlein), as was clearly revealed at necropsy. It appears that from 1893 on, when the patient had her first accouchement, up to the spring of 1918, the calculi had remained either in the gallbladder or in the urachus, while they formed a more or less closed cavity separated from the bladder. Not until this had occurred did the patient discharge successively the one hundred or more stones of which forty-eight were saved. That each group of stones which was passed had not remained long within the bladder is shown by the results of chemical examination, and the same is true of the last stone, the appearance of which was different. The really strange occurrence in the case is that after extraction of this last stone, too large to be evacuated spontaneously, a silent cure took place, the gallbladder having emptied itself completely, without causing infection of either the liver or the bladder.

Hemorrhage.—Boyd [34] stated that sudden, severe hemorrhages into the unopened bladder are usually best treated by emptying the bladder of clots through suitable urethral instruments and then using quite hot irrigations. Electrocoagulation of the bleeding points is sometimes necessary, and occasionally even suprapubic cystotomy may be required. In elderly or anemic patients radical measures should be instituted without too much delay when the hemorrhage is not readily controlled, especially if ample facilities for transfusions of blood are not available for immediate use.

One of Boyd's patients had a hemorrhage into the bladder following an unsuccessful attempt at urethral catheterization, another hemorrhage several days later, which stopped when the bladder was opened suprapubically, and a third hemorrhage a week later, which stopped when the patient was given a spinal anesthesia to permit reexamination of the bladder. Since no visible source of bleeding could be found at cystotomy and since the patient had a fairly large, benign hypertrophy of the prostate gland, Boyd concluded that the hemorrhage was from the veins which ran in the mucosa that covered the intravesical portion of the prostatic hypertrophy. In this instance these veins may have

34. Boyd, M. L.: Severe Hemorrhage into the Bladder, Am. J. Surg. **22**:203 (Nov.) 1933.

been unusually engorged by an obstruction to the venous circulation of the bladder, which it appears could have been caused by an extensive, acute abscess of the appendix which preceded the first hemorrhage by about seven weeks. Unexplained irritation had also appeared just after the appendical abscess was opened and had produced pains in the region of the prostate gland, resulting in spasms of straining to urinate and defecate. These spasms recurred at varying intervals of hours or days and in varying severity for several months, and they were worse during and preceding the hemorrhages. Subsequent examination of the urethra, bladder, rectum and abdomen did not reveal the presence of other changes that could account for the symptoms and the hemorrhages.

Gangrene.—Stirling and Hopkins [35] reviewed 207 cases of gangrene of the bladder, and reported 2 cases of their own. They stated that in any form of severe, chronic cystitis, the possibility of gangrene should be borne in mind and drainage instituted as early as possible. Gangrene of the bladder occurs more commonly than is suspected, because of failure in diagnosis and in obtaining necropsy. Retention of urine and the presence of infection are the chief predisposing factors. Treatment, if instituted early, may result favorably even in the presence of severe necrosis. Palliative treatment may be tried in females, but early drainage by cystotomy offers the best prognosis in males.

Pyo-Urachus.—Stevens [36] reported a case of pyo-urachus which differed from most cases of inflammation of the urachus in that there was no opening leading to the umbilicus or to the bladder; the urachus had not retracted downward as usual but remained attached to the umbilicus. The urachus had remained patent at its upper portion, as proved by the islands of epithelium found. Therefore, the urachus had apparently become merely a cord of smooth muscle and fibrous tissue at the lower end, with no sign of epithelium or of a lumen. The inflammation was confined to the upper part of the urachal structure, without involvement of the vesical end.

PROSTATE GLAND

Prostatectomy.—Harris [37] summarized his experience over a period of five years with his original method of prostatectomy with closure. There have been some minor though important alterations in the technic. The essential features of this operation, which is not to be used by the

35. Stirling, W. C., and Hopkins, G. A.: Gangrene of the Bladder: Review of Two Hundred and Seven Cases: Report of Two Personal Cases, J. Urol. **31**:517 (April) 1934.

36. Stevens, A. R.: Pyo-Urachus, Tr. Am. A. Genito-Urin. Surgeons **26**:13, 1933.

37. Harris, S. H.: Prostatectomy with Closure: Five Years' Experience, Brit. J. Surg. **21**:434 (Jan.) 1934.

surgeon who only occasionally performs a prostatectomy, are: (1) immediate and complete control of hemorrhage by suture, (2) reformation of the prostatic urethra by a trigonal-capsular suture, (3) obliteration of the prostatic cavity by this suture and additional anterior transverse obliterative suture and (4) complete closure of the bladder and abdominal wound. The last-mentioned feature, although a valuable asset, is more of a comfort and convenience to the patient than a vital factor in the final outcome. If the bladder is not completely closed postoperative drainage is of short duration and of no consequence as compared to that in other methods of suprapubic prostatectomy.

Careful attention to all details are essential for success, and there are two factors of safety of paramount importance: (1) employment of surgical asepsis and antisepsis in the care of the catheter in both the preoperative and postoperative periods and (2) employment of the intraurethral method of digital enucleation of the prostate gland. The details of the operation and the special instruments used are described.

Between 1927 and 1932, Harris performed 371 prostatectomies by his plastic method. An operation in one stage was performed in 364 cases, and a two-stage operation in 49. In 356 cases the bladder was closed, and in 15 there was suprapubic drainage. There were 10 deaths, a mortality rate of 2.7 per cent.

Goldstein and Abeshouse[38] reported a case of infection by gas bacilli following perineal prostatectomy. In this case the development of the infection is undetermined. The following sequence of events offers a possible and probable explanation: Clostridium Welchii, which undoubtedly was present in the rectal contents before operation and was isolated from the rectal contents after operation, had spread through the rectovesical and rectoprostatic tissues following the operation and had resulted in an infection of the prostatic bed. The serosanguineous discharge from the operative wound had spread and contaminated the cutaneous surface of the right thigh, and the organism was carried in and implanted in the tissue of the right thigh as a result of hypodermic injections of digalen-Roche (Cloetta).

Familiarity with the clinical symptoms of infection by gas bacilli is essential and imperative in order to recognize and treat this complication successfully. The best results are dependent on early recognition of the disease and on the institution of immediate and thorough treatment. The treatment should consist of wide incision and drainage of the involved areas, including the operative wound, combined with serotherapy. A polyvalent serum injected intramuscularly and intravenously has yielded the best results.

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38. Goldstein, A. E., and Abeshouse, B. S.: Gas Bacillus Infections in Urology, J. Urol. **31**:547 (April) 1934.

Resection.—Caulk and Harris [39] stated that when the various high frequency cutting instruments are used, injury to tissue is often produced more deeply than is generally desirable and that it is often to some extent unavoidable. High current densities applied for more than a second may do injury at depths from a few millimeters to more than a centimeter. In order that tissue may be cut with high frequency currents intense heat is required at the active electrode. To produce this heat it is necessary for the current to pass through the tissue from an indifferent electrode and focalize at this point. In so doing, the paths of current, in their concentration toward the active electrode, generate varying degrees of temperature deep within the tissue, away from the point of active burning; in removal with the actual cautery approximately the same temperature is applied at the surface of the wound, but heat is not produced within the tissue, except by conduction from the surface.

The analysis of Caulk and Harris' experiments with high frequency currents shows conclusively that, at depths within the tissue of at least 1 cm. away from the active point of burning, changes in temperature well beyond the thermal death point of tissue have been produced, whereas with the actual cautery, heat registrations less than 0.5 cm. away, after repeated applications at the same site, have been negligible. The temperature which causes thermal death of tissue cells certainly lies between 44 and 52 C., probably at about 47 C.

An analysis of specimens removed by high frequency excision reveals varying grades of tissue destruction in these distant areas and, according to physical principles, demonstrates more pathologic insult than is noted in the tissue removed by the active electrode, for the simple reason that the current penetration in the underlying tissues is greater than that in the tissue removed. In removal with cautery the opposite is true.

Owing to the inherent quality of electric currents to produce heat in tissue and to the fact that these currents exert a deleterious effect on the tissue well away from the site of burning, it is essential that surgeons who are employing them should recognize their inherent dangers and exercise every precaution in modeling their technic. Bearing these points in mind, it is absolutely necessary in resection of the prostate gland to shift the scene of activity from one portion of the gland to another, in order to deviate the paths of current, avoid accumulative heating and not concentrate on any one segment except for a short time. It is also highly important that the minimal cutting current be applied for

39. Caulk, J. R., and Harris, Wilbur: A Study of Comparative Effects of Various High Frequency Currents and of Thermal Cauterization in Prostatic Resection, Tr. Am. A. Genito-Urin. Surgeons **26**:168, 1933.

the shortest possible time. If bleeding should occur it should be controlled with coagulating currents, which are far less penetrating and injurious. Removal of prostatic obstruction by cautery, or by methods which involve mild coagulation followed by excision of tissue or by cold cutting procedures followed by coagulation, unquestionably appears to have less inherent dangers than methods which employ any type of high frequency cutting.

URETHRA

Urethrotomy.—Barney [40] reported a simple method of performing external perineal urethrotomy which he has used successfully over a period of fifteen years. A soft rubber catheter is passed through the urethra into the bladder in the usual manner until its distal or outer end is almost level with the external meatus or with the orifice of the urethra. That end of the catheter is then grasped with a small clamp, preferably with a half-curved shank. The catheter and clamp are then passed on into the urethra until the point of the clamp can be felt pressing against the floor of the bulb. In the meantime, the free portion of the catheter has passed on into the bladder. The point of the clamp is now made to impinge against the perineum, bulging it sharply outward in the median line. An incision from 1 to 2 cm. in length is then made through the median raphe, the tissues being divided until the point of the clamp, the catheter still in its grasp, is exposed and worked through the incision. The end of the catheter is then firmly held with the fingers or by another clamp, the first clamp being opened and withdrawn backward from the urethra, leaving the catheter emerging from the perineal incision. The catheter is then drawn out until its eye occupies a suitable position within the bladder for uninterrupted drainage. Two transverse sutures are taken, one above and the other below the catheter, each being tied around it. These sutures should be passed quite deeply so as to include the corpus spongiosum, thus not only controlling whatever bleeding there may be, but also anchoring the catheter firmly in place. Care should be taken that while being passed through the urethra the clamp is not permitted to open and release the end of the catheter.

Formation of Valve.—Lowsley and Kirwin [41] stated that Young and his co-workers distinguished three general types of valve formation causing obstruction of the urethra, a classification which has been used by later writers on the same subject. In type 1 there is a ridge on the

40. Barney, J. D.: A Simple Method of Performing External Perineal Urethrotomy, Surg., Gynec. & Obst. **59**:100 (July) 1934.

41. Lowsley, O. S., and Kirwin, T. J.: A Clinical and Pathological Study of Congenital Obstruction of the Urethra: Report of Four Cases, J. Urol. **31**:497 (April) 1934.

floor of the posterior urethra, commencing at the verumontanum and continuing as a part of this structure. This ridge runs anteriorly to the bulbomembranous juncture where it divides into two processes, which are attached, in the form of a thin membrane, to the circumference of the urethra, at times completely encircling it. In type 2 there are similar membranous sheets, attached posteriorly to the verumontanum, in the region of the internal sphincter. In type 3 the membranes are without any relation to the verumontanum; these may be found in any portion of the posterior urethra. This type is called the "iris valve" because the valve resembles the iris of the eye. The membranous structure fills the entire circumference of the urethral lumen, but there is a small opening in its center; at times this is very minute or of such dimensions as to give the appearance of two folds lying at either side. The concave aspect of this form of membranous obstruction is always toward the bladder.

The symptoms of this lesion are manifested by the immediate effects of obstruction to the outflow of urine and by the more remote consequences of back pressure and urinary retention. The symptoms may be only those of secondary infection, the general condition resembling that seen in hypertrophy of the prostate gland. The most common symptom is a small urinary stream of diminished force, with straining and difficulty. The distended bladder is often palpable as high as the symphysis. Overflow incontinence, with a history of urinary difficulty or a previous diagnosis of enuresis, is likely to be the characteristic finding. In the advanced cases more distinct effects of the chronic obstruction to vesical drainage are observed. The clinical picture may simulate that of chronic diffuse nephritis or it may suggest the syndrome accompanying bilateral polycystic kidneys. In general, the symptoms are those of long-continued retention of urine and of infection.

There is a divergence of opinion as to the best method of eliminating these obstructions, although there is complete agreement as to the necessity of their immediate and entire removal. The condition is closely analogous to retention in hypertrophy of the prostate gland among men of middle age. Proper preliminary treatment of this condition among children is as important as suitable operative measures. In the first cases recognized attempts were sometimes made to dilate the obstruction forcibly with sounds, or the urethrotome was frequently used. In a few of his earlier cases Young performed operation intra-urethrally, using the punch instrument. Randall successfully employed fulguration in 2 cases. Hinman and Kutzmann followed several different plans of treatment in their 6 cases, among others, suprapubic cystotomy and perineal prostatectomy, with destruction of valves in the posterior urethra, or suprapubic cystotomy with splitting of the urethral folds.

A man aged 57 and an infant aged 2 years both presented median bars which were resected suprapubically; in other cases fulguration was used.

Tumor.—Lazarus [42] stated that carcinoma of the urethra is relatively rare. Any long-standing stricture of the urethra that does not yield to the usual methods of dilation and that is accompanied by a hemorrhagic urethral discharge should be thoroughly investigated. A stricture involving the membranous portion of the urethra, accompanied by a periurethral abscess which fails to respond to the usual methods of treatment, is also indicative of the possibility of carcinoma. A stricture of the urethra accompanied by a region of induration within the urethra, especially when accompanied by inguinal lymphadenopathy, suggests carcinoma, and biopsy should be made on a node removed from the groin. The treatment of choice is radical amputation of the penis, with block dissection of the inguinal and crural lymph nodes, followed by radiotherapy. The prognosis in cases of carcinoma of the urethra is poor, principally because of failure to make an early diagnosis.

TESTES

Undescended.—In 1926, Burdick and Coley [43] reviewed the operations for undescended testes at the New York Society for the Relief of the Ruptured and Crippled and were so discouraged with their end-results that they sought some better method of operating. Torek's results by orchiopexy, bringing the testis out through an incision in the scrotum, anchoring it to the fascia of the thigh and suturing the margins of the scrotal wound with those of the thigh, were so satisfactory that Burdick and Coley tried his method. They tried it first in selected cases, and they were so pleased with the results that they have adopted it as a routine procedure during the past five years at the New York Society for the Relief of the Ruptured and Crippled, in the children's surgical service of Bellevue Hospital and at the Lincoln Hospital. Burdick and Coley believe that the most suitable age for operation is between 8 and 12 years. This gives the testis a good chance to descend voluntarily if it will; it is larger and easier to manipulate, and the structures are more easily identified than among younger patients. Also, the organ has been placed in its normal position before the changes occur which come with puberty.

Burdick and Coley believed that if the undescended or maldescended testis is accompanied by a large hernia, an earlier operation is imperative, as, naturally, retention of the hernia by a truss is certain to exert pressure on an already underdeveloped organ and also prevents any tendency

42. Lazarus, J. A.: Primary Carcinoma of the Male Urethra, J. Urol. **31**: 823 (June) 1934.

43. Burdick, C. G., and Coley, B. L.: Undescended Testicle, Ann. Surg. **98**: 495 (Oct.) 1933.

to normal descent. Moreover, the continued trauma of a truss may, theoretically at least, predispose to malignant change in the undescended testis which, statistics have shown, is more prone to such degeneration than a normally situated testis. Trusses, therefore, are contraindicated. In cases of maldescent, especially when the testis is directed into the thigh instead of the scrotum, Burdick and Coley usually advised operation earlier, as further descent does not aid the testis in reaching the scrotum.

Torek's operation is described in detail; it consists principally of freeing the testis, lengthening the spermatic cord and then anchoring the testis to the thigh. This anchor is released at a second operation, when the scrotum has been sufficiently lengthened. In reviewing their operations by the Torek method Burdick and Coley were impressed by the fact that many times a testis which was only half or two-thirds normal size at the first operation had developed, and, at the second stage, approximated normal size. Other testes that had not been normal at this stage had continued to develop in the scrotum, and a follow-up note a year later elicited the information that the testis operated on was the same size as its fellow. Not infrequently it is difficult to palpate a testis buried in the thigh, and its actual size cannot be appreciated. In several instances in which Burdick and Coley thought that the testis was greatly atrophied they were surprised to find, after dissecting the organ from its bed in the thigh, that it had developed to normal proportions.

Burdick and Coley stated that they have completed 137 cases for final analysis; in 123, the results were excellent. The testis was normal in size and was lying free in the bottom of the scrotum. The scars in the region of the groin and thigh were the only evidences of a previously undescended testis. Their failures were due to technical errors; sufficient care was not used in dividing all the fascial bands, or the vessels were not sufficiently mobilized to permit the testis to be sutured to the thigh without tension. In a few cases the scrotum was sutured to the thigh in a position which caused too much tension on the suture line, so that the scrotum became partly or completely separated from the thigh. Five testes sloughed; 2 of these were sutured to the thigh without tension, but the suture line became infected, and the scrotum separated completely from the thigh. This separation, added to the infection, undoubtedly caused the sloughing. The other 3 were sutured to the thigh under too much tension. Nine were reported to be atrophic, and in 3 there was complete atrophy. One patient was discharged with a testis almost normal in size, but a follow-up note received one year later stated that the testis had atrophied and could not be palpated.

Burdick and Coley concluded that failures by Torek's method of orchiopexy can usually be attributed to some technical error. In their hands, so far, the end-results have been superior to those which they obtained by the former methods; they therefore do not feel justified in using any other type of operation.

Coley [44] stated that among 80,736 cases of inguinal hernia in males observed at the New York Society for the Relief of the Ruptured and Crippled, he found 1,357, or 1.65 per cent, in which the condition was associated with undescended or maldescended testes. From 1890 to 1918 operation had been performed in 4,453 cases of inguinal hernia of the male and in 334, or 7.5 per cent, of these cases the condition was associated with undescended testes. In the majority of these cases the condition occurred in children less than 14 years of age, inasmuch as in the earlier days adult patients with hernia were not admitted to the hospital. Of the 1,040 cases of hernia in adults in which operation was performed at the Memorial Hospital for the Treatment of Cancer and Allied Diseases by William A. Downes and by Coley, 49, or 4.71 per cent, were associated with undescended testis. The method of operation adopted by W. T. Bull and by Coley in 1892 and 1893 was, practically, the Bassini operation. However, they omitted the step of transplanting the cord, thus adding ½ inch (1.2 cm.) or more to its length. In addition, the cord was freed as high up as possible, and the bands of fascia, which usually made it possible to place the testis in the bottom of the scrotum, were divided. At about the same time, and quite independently, Bevan developed his operation for the undescended testis, which embodied the principles just described and had several additional features that were improvements over the method of Bull and Coley. One of these was purse-string sutures of the tissues just outside the external ring which prevented the testis from retracting into the canal or above the external oblique muscle. The second feature of Bevan's operation was the removal of a part or almost all of the veins of the cord. This naturally added to the length of the cord and to the possibility of placing it at the bottom of the scrotum without much tension. Bevan himself restricted excision of the veins to very difficult cases, and he did not use it as a routine operation.

In 1908 Coley reported his end-results of operation in 126 cases of undescended testis. Ten years later he reported 365 cases of undescended testis in which operation was performed by Downes and himself at other hospitals, making a total of 415 cases. Twenty-seven were of inguinosuperficial type and 8 of inguinoperineal type; 149 patients were traced from one to twenty years after operation. While the results were, in their opinion, reasonably satisfactory, they were not ideal, since in a considerable number of cases the testis retracted

44. In discussion on Burdick and Coley.[43]

to the region of the external ring. There was no case of death or of recurrence of the hernia in the entire series. In reviewing the entire question, it seemed to Coley that it might be better to admit that the results obtained by the Torek operation are more satisfactory than those obtained by the older methods. At the same time he advised reserving the Torek method for the group of more difficult cases in which it is almost impossible to place the testis in the bottom of the scrotum without great tension and advocated that in the larger group of less difficult cases the Bevan operation, which has proved so highly satisfactory, be used.

There is still some difference of opinion as to the proper age for operating. Many years ago, Coley adopted the plan of waiting until the patient had reached the age of 10 or 12 years, unless there was some special reason for earlier operation, such as hernia which was not easily controlled. He still follows this plan, although some surgeons advise operating on patients as young as from 5 to 6 years. Coley's principal objection to the earlier operation is based on the fact that, in a considerable number of cases, the testis has descended of its own accord as the child has approached puberty. Some surgeons advocate removal of the undescended testis on the ground that it is of no special value. Although most writers regard it of no functional value there is no question but that the interstitial elements of the testis have an important bearing on the development of the male characteristics of the child, and for that reason Coley believes that the testis should not be removed. It is by no means true that the undescended testis is always functionless. He had 2 patients with bilateral undescended testes who married and had children.

Bevan [44] stated that the purpose of operations for undescended testis is to accomplish in the period required to perform the operation, possibly in an hour, what nature does slowly and gradually in the normal descent of the testis in a period of weeks and months. Many men who have undertaken these operations have not had a complete conception of the anatomy or of the technic required to perform the operation successfully. It is absolutely essential that the operator should know that when freeing the testis it is necessary to remove completely from the cord the structures which surround the testis and the cord, namely, the intercolumnar fascia, the cremasteric muscle fascia and the infundibuliform fascia, as well as to strip the cord completely of the vaginal process of peritoneum. Bevan has performed these operations in a large series of cases. He could not see any fair indication for complicating the operation of undescended testis with any scheme of suturing the testis to the thigh or of holding the testis down with traction sutures of any kind during the process of repair.

Before undertaking work of this kind the surgeon should know that there is a certain proportion of cases, possibly 10 per cent, in which the organs are so poorly developed, the structures of the cord so short, or the testis so far up in the abdominal cavity, that it is impossible to bring the testis down and place it in its normal position by any method of operation. Some of these rudimentary testes are best removed. Occasionally, when the cord is very short and the testis otherwise fairly normal, it may become necessary to divide the spermatic vessels in order to lengthen the cord sufficiently to place the testis in its normal position in the scrotum. Bevan seldom divided the vessels, and yet undoubtedly, in a limited number of cases, it is better to do this than to drop the testis back into the abdominal cavity or to remove it, because in a fair proportion of cases in which operation was performed in early life, even though the vessels are divided, the blood supply is sufficient to carry on the nutrition of the organ. If these testes are operated on when the patients are 5 or 6 years of age, which is probably the most favorable age, the operation can be performed very easily; most of the testes can be brought well down. The time to operate in these cases is early, long before puberty. It does not do any good to operate after puberty except for the psychic effect and for the cure of associated hernia.

Torek [44] stated that it was quite natural that every surgeon should select the technic that appealed to him and the one he was most accustomed to employ. In regard to attachment of the scrotum to the thigh by a subcuticular continuous suture, Torek has always used the interrupted suture through skin and subcutaneous tissue, and he tries to obtain broad apposition of raw tissue; this is done by taking very little skin and a good deal of raw tissue in adapting the parts. He considered that in this operation just as in any operation, especially in plastic surgery, it is important to obtain a very accurate apposition which leads to the most prompt and certain healing. Consequently, he has continued to use suture through the skin and subcutaneous tissue, and he has had no reason for deviating from this method of suture because, in his case, the scrotum has always remained attached. With the other method there were 2 cases in which it became loosened. Another point, not technical but fundamental, is the attachment of the testis to the fascia of the thigh, not by interposition of any other structure, but by direct attachment. The reason he considered this to be of fundamental importance is that, at least in the difficult cases, surgeons have to deal with a rudimentary testis or with a very poorly developed one. These badly developed testes usually have very small and short vessels, so that probably they are not well nourished from their own vessels, and attachment to the thigh gives the testis a new supply of blood. It is possible

that addition of this supply from a new source has something to do with the fact that in all their cases the testes have increased in size.

The matter of bringing both sides down at the same time has been mentioned. Torek admitted that there may be some cases in which this procedure is possible. However, he did not think that when surgeons have to deal with an absolutely rudimentary scrotum it would occur to them to try that method, because there is not enough skin to go across from one side to the other.

Lyle [44] called attention to the fact that the pull to which the testis is subjected in the Torek operation seems to have a stimulating effect on the opposite testis. He cited one of his cases of bilateral undescended testis in which, during the first stage of the Torek operation, the opposite testis descended into the scrotum. Since then he has observed this phenomenon in 2 additional cases. Regarding the applicability of this operation to the abdominal testis, one of his assistants has successfully transplanted such a testis to the bottom of the scrotum in three stages. In the first stage the testis was brought to the pubis, in the second to the thigh, and in the third stage, to the bottom of the scrotum. In this position the testis had developed and appeared to be normal.

Eggers [44] stated that other methods of traction have the disadvantage of leaving a canal at the bottom of the scrotum through which infection may enter. In children that is an important point. Torek's method is a closed one; it is strictly surgical, and it is a very delicate operation. In children great care has to be taken in handling the organ; the surgeon must not be rough, and if this caution is observed the results are excellent.

Eggers has performed the operation thirty times, and in all the cases the results were very satisfactory. There is a well developed pendulous scrotum, and the testis is situated at the lower part of the scrotum. In cases of bilateral undescended testes he always performs the operation in two stages because it has to be done carefully and it takes time, frequently as long as an hour and a half. There must be no undue tension on either the scrotum or the testis, and this is best accomplished by operating on one side at a time. The organs have a better chance to accommodate. At the first operation one testis is brought down; the next operation is performed about six months later, when the first side is separated and the other side is brought down. The third operation consists simply of separating the second side. There is no definite period which should be allowed between operations. Eggers has found that six months is sufficient time to allow the organs to accommodate themselves to their new position. Retraction of a testis has never occurred.

Gibbon [44] emphasized two points which he considered of primary importance irrespective of the type of operation performed: 1. The

necessity of freeing the component parts of the cord from surrounding tissues and from one another, which is the only way in which the testis can be brought down without tension. Mere cross-section of the sac and high removal of the proximal portion is but the first step in the mobilization. 2. Preservation of the blood vessels, even the veins, because in applying ligatures the tiny but essential arteries may be included. On this point depend the future position and development of the testis.

In his treatment of undescended testis Starr [44] frees the cord and sutures the tunica of the testis to it with a silver wire. Then after the scrotum has been stretched, the testis is placed in the bottom of the scrotum. The two wires are brought out of a nick at the bottom of the scrotum, and each is turned transversely; two horsehair stitches catch it there, and a loop at the other end is then sutured by fine catgut to the periosteum in the os pubis. His results have been unusually good.

Testicular Function.—Lower [45] stated that the fact that structure and function of the prostate gland are dependent on the endocrine activity of the testes is well known. Following castration the prostate gland becomes atrophic. Moore and his collaborators have demonstrated that the hormone extracted from the testis maintains the prostate gland in an apparently normal condition following castration. A series of experiments performed by Lower indicated that preparations of the male sex hormone will prevent atrophy of the prostate gland and seminal vesicles in castrated rats. In the complete absence of the hypophysis preparations of the male sex hormone will prevent regressive changes in the prostate gland and seminal vesicles and also in the testes. Experiments with parabiotic animals indicated that the hyperactivity of the pituitary gland occurring in the castrated partner may be modified by injections of testicular mush.

EPIDIDYMIS

Infection.—Buckingham,[46] in discussing nonspecific metastatic epididymitis, stated that bacteria may enter the blood stream from any focus during the course of infectious disease and may lodge in tissue and set up a reaction there. The end-result in any given case depends on the number of bacteria set free, the virulence, the susceptibility of the host and the specific localizing tissue. Because of its close embryologic relationship to the kidneys the epididymis tends to localize bacteria. Direct trauma plays an important part in the localization in the epididymis. The condition is seen most often during the course of respiratory infections. Any swelling of the epididymis without evidence of involvement of the

45. Lower, W. E.: The Exocrine and Endocrine Functions of the Testes, J. Urol. **31**:391 (March) 1934.

46. Buckingham, W. W.: Non-Specific Metastatic Epididymitis, J. Urol. **31**: 87 (Jan.) 1934.

genito-urinary tract indicates that infection has occurred by a metastatic route; thus a specific focus should be looked for and treated. After thirty-six hours of expectant treatment without benefit, incision and drainage should be performed in the acute cases and epididymectomy in cases of the pseudotuberculous type.

SCROTUM

Filariasis.—Young [47] reported 5 cases of filariasis of the scrotum and groin, 4 of which are quite alike. One, an ordinary case of chronic epididymitis following cystoscopy, is presented as a contrast to the other 4 cases. The patient in this case came from the same locality in Colombia, South America, as the others, but he presented entirely different lesions. The first 3 cases and the fifth, which are cited in detail, are remarkable in that the disease did not start in the testis, epididymis, vas deferens or vessels of the cord, but as a peritesticular or periepididymal disease. It was characterized by the ultimate formation of a dense mass of tissue, which in 2 cases had completely enveloped and compressed the epididymis without involving its tissues.

From its point of onset in the coverings of the epididymis or testis the disease has always traveled upward outside the spermatic cord. The filariae and surrounding inflammatory tissue become more or less loosely attached to the external fascia of the cord, in some instances forming large, globular masses, and in others, very fine lines suggesting lymphatic structures with small, beadlike enlargements along the course of the lymphatics. The presence of enlarged inguinal glands has been noted.

In none of the tissues removed has Young been able to find evidence of any ordinary bacterial inflammation, of tuberculosis, syphilis or malignant disease. The pathologic process was characterized particularly by the deposit or growth of large numbers of round cells, which ultimately had gone on to the formation of a marked fibrous sheath or covering. In some instances the tunica vaginalis was extensively involved, with adhesions to the testis, but the testis itself was free from disease, although in 1 case it was compressed and distorted by the fibrous tissue. The intrascrotal cord produced by the disease was characterized also by the presence of much vascularity, and around the walls of the blood vessels were numerous areas of round cell infiltration. These spaces might have been lymphatic channels, although in stained sections they were not seen to contain material, and nothing suggesting a large or small worm, larva or detritus resulting from the presence of a dead worm had been found. Nevertheless, it seemed evident that the disease was of filarial origin.

47. Young, H. H.: Some Unusual Cases of Filariasis of the Scrotum and Groin, Tr. Am. A. Genito-Urin. Surgeons **26**:120, 1933.

In the first case the numerous enlarged glands in various parts of the body of a man who had no evidence of syphilis were suggestive of filariasis, and in the second case, the presence of filariae in several members of the family, going back a generation or more, was presumptive evidence that this disease was the etiologic factor. Young stated that the condition may possibly be due to some process that has not been described before; he based his statement on the facts that nowhere in the literature had he been able to find exactly the same conditions he found in these cases and that filariae were not discovered.

Young believed that the disease is due to filariae, and that Onchocerca volvulus is probably the causative factor. His experience reveals that a radical operation should be performed in these cases, as the results he obtained have been very satisfactory.

VAGINAL STONE

Masson and Appell [48] stated that calculus of the vagina is a rare condition, only 20 cases having been described in the literature; to these they added 2 more. This condition occasionally develops in association with vesicovaginal fistula, foreign bodies, stagnation of urine due to paraplegia and enuresis, calcified fibroid tumors which had migrated into the vagina and vaginal cysts. In some cases the cause was unknown. The stones were all composed of urinary salts, except those which were due to calcified fibroid tumors.

The symptoms are urinary incontinence, pelvic and perineal pain and fetid vaginal discharge with occasional bleeding and dyspareunia. The stone is usually felt in the vagina and is easily removed digitally, except in rare cases in which the vaginal orifice is contracted or completely closed. In such cases some type of operation on the vaginal outlet is necessary. Removal of the stone and repair of the fistula, followed by irrigations of the bladder and vagina when indicated, usually give complete relief.

URINARY INFECTIONS

Band, Dunlop and Dick [49] reported the results of their studies of infection of the urinary tract from the pathologic, therapeutic and bacteriologic standpoints. Band demonstrated the pathologic changes in the various types and stages of infections: acute pyelonephritis with resolution and with suppuration, paths of intraparenchymatous reinfection, chronic pyelonephritis with suppuration and with fibrous tissue replacement of tubules and glomeruli and atony and dilatation of the pelvis and calices, and pyonephrosis. These are best illustrated by

48. Masson, J. C., and Appell, A. A.: Vaginal Calculi, West. J. Surg. **42**: 132 (March) 1934.

49. Band, David; Dunlop, D. M., and Dick, I. L.: Studies in Urinary Infection. Pathological, Therapeutic and Bacteriological, Edinburgh M. J. **40**:65 (May) 1933.

"whole sections" of the kidney. Focal infection throughout the body may be followed by metastasis to the urinary tract. In 77 per cent of Band, Dunlop and Dick's cases the infecting organism was Bacillus coli, and the large intestine was the principal source of infection.

In a consideration of the descending infections it has been noted that, prior to their onset, there have been signs and symptoms of alimentary disturbance with evidence of renal irritation, albuminuria and an excess of oxalates, urates or phosphates, indicating a metabolic disturbance. It is suggested that the kidney is injured by a bacterial or chemical toxin prior to the onset of infection. This has been confirmed by experiments which show that, after inoculation of the blood stream with B. coli, pyelonephritis is not easily produced unless the kidney has been injured previously by a bacterial or chemical toxin.

Ascending infections from the lower part of the urinary tract have been shown to occur through the wall of the ureter in the periureteral lymphatic structures. It is doubtful whether ascending infections ever progress through the lumen of the ureter when the ureteral orifices are competent.

Several factors contribute to the pyelonephritis of pregnancy. Pelvic and ureteral atony and dilatation from changes in the circulation and innervation of the pelvic viscera, including the pelvic portion of the ureter, may occur. The unknown toxins of pregnancy, which in addition, produce renal irritation contribute to the condition. This combination makes the kidney a fertile field for blood-borne infection during pregnancy.

The care of infections in the urinary tract is modified by the contributing lesions and the stage and type of the infection. Chief interest lies in notoriously resistant, subacute, chronic and recurring pyelonephritis and cystitis. This stage has been arrived at as a result of : (1) the existence of a source of reinfection outside the urinary tract, (2) the presence of stasis within the urinary tract, which permits the organism to multiply and adapt itself to conditions there and (3) residual infection in the renal parenchyma, which has been recognized as a localized area of congestion and small cell accumulation surrounding a disorganized tubule. Such an area tends to remain active and unhealed while the circulation and drainage of the renal parenchyma are deficient.

Particular attention should be paid to the alimentary tract as a source of infection in the care of infections of the urinary tract as a whole. In the direct attack on the urinary tract the object should be: (1) to encourage and aid drainage of the renal pelvis and (2) to increase the bactericidal qualities of the urine. The first is best accomplished by repeated pelvic lavage. The second is obtained by lowering the p_H of the urine by the ketogenic diet, using the ammonium salts and causing

diuresis by the ingestion of large quantities of water, so that the output of urine reaches 3,000 cc. in twenty-four hours.

One hundred and thirty-six cases of pyelocystitis are analyzed as to the nature of the infection, sex incidence, average duration of symptoms and end-results. Twenty-three patients, or 17 per cent, were unimproved by the ordinary methods of treatment, and this "intractable" group were hospitalized and put on the ketogenic diet without other treatment. The management of, and the results obtained in, this group are analyzed by Dunlop. He concluded that ketonuria has strong bactericidal powers and that in the future this diet may be used in the treatment of intractable, chronic pyelocystitis. He also emphasized the drawbacks. It requires hospitalization, close clinical control of the patient and a competent dietitian. Not all patients can take the diet, and it is not invariably successful, although it may be used when other methods have failed and may yield very successful results.

Following bacteriologic researches to measure the bactericidal properties of ketonuria and to determine whether these properties are due to changes caused by the diet in the reaction of the urine or to some unknown antiseptic substance, Dick concluded that: 1. Ketonuria has a bacteriostatic effect, at least for the type of organism used. 2. This effect is not entirely due to an increase in the acidity of the urine. 3. It is still sub judice whether a certain degree of acidity is essential for the production of this bacteriostatic effect. 4. Any evidence as to the nature of the active substance is, so far, only of a negative kind.

Campbell,[50] in discussing chronic pyuria of juveniles, stated that it usually indicates a potentially serious urologic disease. It is seldom due to uncomplicated infection in the urinary tract. The methods of diagnosis and treatment are identical for juveniles and for adults. The diagnosis can be made only by a careful, complete urologic examination. The treatment often requires radical surgical attack. By properly directed urologic treatment, a gratifying number of juvenile patients may be cured. A much larger number will be improved and the renal destruction greatly diminished or checked. Nearly all the others can be made more comfortable. Campbell is convinced that it is the duty of all urologists to bring these facts more forcibly to the attention of the medical advisers of the young.

McCarthy and Ritter [51] discussed 293 cases which were referred for bacteriophage therapy. Bacteriophage was obtained in 112 of these cases. Definite data were secured in 69 cases, of which 43 were excluded for the following reasons: It was found that results were

50. Campbell, M. F.: Chronic Pyuria in Juveniles, J. Urol. **31**:205 (Feb.) 1934.

51. McCarthy, J. F., and Ritter, J. S.: Bacteriophage in Genito-Urinary Tract Infections, Tr. Am. A. Genito-Urin. Surgeons **26**:123, 1933.

negative in 16 of the 69 cases; patients were resistant after treatment in 3; symptomatic improvement was present in 24 (not bacteria-free), and symptomatic and bacteriologic cures were obtained in 25, or more than 36 per cent of the cases.

Of 16 patients with staphylococcic septicemia, most of whom were cared for in other departments of the hospital, 6 have recovered following treatment with bacteriophage, which is most unusual in so grave a condition. McCarthy and Ritter stated, however, that in a certain percentage of cases of apparent cure later cultures of the same or of other bacteria have been developed.

HEMATURIA

Debenham [52] has analyzed 742 consecutive cases of hematuria among patients in the genito-urinary department of the London Hospital from 1924 to 1930. He reported the findings under the following headings: (1) general consideration of the causes of hematuria, sex incidence, severity of the bleeding and common causes thereof; (2) consideration of the various conditions giving rise to hematuria and relative importance of evaluation of the main symptoms, and (3) consideration of the unexplained cases with results of the follow-up investigation.

Only patients with gross hematuria were included in the study. Each patient was subjected to the various steps of a complete urologic study, as indicated by the objective findings.

Cystoscopic examination is important during hemorrhage. From this study it was found that papilloma and carcinoma of the bladder are the most common causes of hematuria among men and that inflammatory conditions of the urinary tract are the most common causes of hematuria among women. When hematuria is a presenting symptom among men, there is a 50 per cent possibility that it is due to papilloma or carcinoma of the bladder. Among women the cause is as likely to be inflammation as neoplasm. With hematuria as the only symptom in 65 men, there was a two to one chance that the condition was due to papilloma or to carcinoma of the bladder. Among women (10 cases) the most common cause was renal calculus. In men over 50 years of age the prostate gland is a common cause of hematuria. In 130 cases of hematuria of men over 60, 43 per cent were suffering from papilloma or carcinoma of the bladder and 37 per cent from simple or malignant enlargement of the prostate gland. Carcinoma of the bladder is not infrequently associated with enlargement of the prostate gland; in some cases the symptoms are rather similar, and, unless cystoscopy is performed, the case may for a time be considered to be one of prostatic enlargement, and valuable time may thus be lost.

52. Debenham, R. K.: An Investigation of Seven Hundred and Forty-Two Cases of Haematuria, Brit. J. Surg. **21**:44 (July) 1933.

The common causes of hematuria in the different decades of life are given on a chart. The conclusion is that hematuria is rare in the first two decades of life. In the second and third decades inflammatory conditions and calculi are the most common causes in both sexes. Neoplasm becomes the most common cause of hematuria among men in the fifth decade and in both sexes in the sixth decade of life.

Carcinoma of the kidney is rare; it was the cause of only 2.5 per cent of all the cases of hematuria (men, 3 per cent, women, less than 0.5 per cent).

Renal calculi not uncommonly cause hematuria, which may be almost or quite painless.

The diagnosis of hematuria due to varicose vesical veins must be made with great caution, unless the bleeding is actually seen to be coming from a varix.

In the 66 cases of unexplained hematuria, 49 patients were traced and the after-history discovered, and in 4 (8 per cent) of these the patients reported that calculi had either been passed or removed. Thirty-three patients (67 per cent) were almost or quite well, further bleeding not having occurred. Eight patients (16 per cent) reported a recurrence of bleeding on one or more occasions. All were well or only slightly inconvenienced, except a man who had syphilis and who had become blind. Four patients (8 per cent) had died, 2 of acute pulmonary conditions not connected with the hematuria, 1 of carcinoma of the prostate gland eight years after his attendance at the hospital, and 1 of apoplexy.

The most difficult cases to diagnose are those in which there are few symptoms other than the hematuria which has ceased by the time the patient comes to the hospital. Cases of unexplained hematuria fall into several different categories; the prognosis is good if nothing abnormal can be found on full urologic investigation.

ANESTHESIA

Rovenstine [53] reported a study of spinal and transsacral anesthesia in cases of transurethral resection of the prostate gland, which is of value in further work for this surgical technic. Transurethral resection of the prostate gland is a major surgical procedure so far as anesthesia is concerned, and the same complications may be anticipated as those which occur when the gland is enucleated.

Spinal anesthesia, with procaine hydrochloride skilfully administered, is satisfactory. The complications which are generally recognized to contraindicate its use are involvement of the central nervous system,

53. Rovenstine, E. A.: Anesthesia for Transurethral Prostatic Resection. A Comparative Study of Transsacral and Spinal Blocks, J. Urol. **31**:633 (May) 1934.

turbidity of the spinal fluid, the presence of a lesion at the site of injection, a markedly diminished vital capacity or extreme variations from the normal blood pressure. Anesthesia with spinal block should not be permitted to affect intercostal activity. Advantage should be taken of methods to insure proper placing of the anesthetic solution in the lumbar region, namely, position of the patient, injection in the most caudal interspace accessible, slow rate of injection, an amount of diluent for procaine hydrochloride in the ratio of 1 cc. for each 100 mg. of the drug, and the important addition of dextrose to the solution of spinal fluid and procaine hydrochloride.

The amount of procaine hydrochloride used in this series of spinal block operations was excessive. Doses of from 50 to 75 mg. are sufficient for more than an hour of anesthesia if properly injected, and more than 100 mg. should never be required.

Transsacral block anesthesia with procaine hydrochloride and epinephrine gives satisfactory results. It requires skill on the part of the anesthetist and must be done completely in every case. The difficulties encountered are usually due to the wide variation of the sacrum in different persons. The shape and structure of the bone vary with individual characteristics of bodily build and from changes due to metabolic diseases. The total amount of solution needed depends on the time necessary for the operation. In this series too much was often used. In practically all cases a total of from 40 to 50 cc. of 1 per cent solution of procaine hydrochloride with epinephrine (1:1,000), 5 minims (0.3 cc.) per hundred cubic centimeters, properly placed, suffices for two hours of satisfactory anesthesia. Contraindications to transsacral block, namely, a lesion at the point of injection and idiosyncrasy to procaine hydrochloride, are fewer than with spinal block. In transsacral block it is imperative to delay the operation until the anesthetic agent has had at least twenty minutes to exert its action. Sacral nerves carry a layer of dura mater throughout their length through the sacral foramina, retarding the action of drugs and making for slow penetration. For this reason, and to allow the anesthetist an opportunity to observe the patient's reaction to procaine hydrochloride and epinephrine, the injection should be made slowly. Proper transsacral block cannot be accomplished in less than fifteen minutes, and more time should be allowed for safety.

Preliminary medication was overdone in this series. The administration of derivatives of barbituric acid preoperatively is advantageous as a prophylaxis to toxicity caused by procaine hydrochloride, but their use night and morning is hardly warranted. A barbiturate at night and morphine or morphine combined with atropine or scopolamine hydrobromide were unnecessary in this group. Patients of the average

age in this series have a metabolism curve near the base line, require less psychic sedation and are more susceptible to hypnotic and to sedative drugs than the average, active person. A short-acting derivative of barbituric acid such as pentobarbital-sodium in small doses, ½ grain (0.032 Gm.), given approximately thirty minutes before anesthesia is started suffices in most cases.

The anesthetic agents and the technic used in cases of transurethral resection of the prostate gland are not nearly so important in securing satisfactory results as are the keen judgment, technical skill and experience of the anesthetist.

Hess [54] stated that epidural anesthesia is ideal for operations on the kidney and upper part of the ureter when the general condition of the patient is such that other forms are contraindicated or dangerous. It should not be used as a routine procedure, however. In his experience there have been no postoperative complications from its use. A large percentage of the patients operated on complained of discomfort during the operation, but it is considered the safest of all procedures.

Foulds and Douglas [55] stated that the field of usefulness of spinal anesthesia increases in proportion to the familiarity with the method. The contraindications have diminished as experience with this type of anesthesia has been gained. Since ephedrine has been used as a routine the number of cases in which the fall in blood pressure has been alarming has been reduced to a minimum, and the contraindications to spinal anesthesia in hypotension have been removed. By selecting cases suitable for each drug the results have improved. Although procaine hydrochloride in doses up to 150 mg. is suitable for operations on the lower part of the urinary tract, untoward symptoms frequently follow the administration of larger doses for higher and longer anesthesia. Such anesthesia for renal operation can be more perfectly obtained with fewer unpleasant symptoms by the use of nupercaine in doses up to 20 cc. of a 1:1,500 solution. The postanesthetic sequelae have been negligible and the postoperative complications fewer than with general anesthesia. Spinal anesthesia is considered by Foulds and Douglas to be the best choice in the majority of operations on the genito-urinary tract.

Abeshouse [56] stated that, in a period of forty months at Sinai Hospital, spinal anesthesia was used in 327 operations on the genito-urinary tract. This series of operations included 27 resections of the prostate gland.

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54. Hess, Elmer: Epidural Anesthesia in Urological Surgery, J. Urol. **31**:621 (May) 1934.

55. Foulds, G. S., and Douglas, H. S.: Spinal Anesthesia in Urology, J. Urol. **31**:607 (May) 1934.

56. Abeshouse, B. S.: In discussion on Foulds and Douglas,[55] p. 615.

Twenty-four patients died following operation, an average operative mortality of 7.3 per cent. Only 1 operative death could be attributed directly to the spinal anesthesia. In this case the anesthetic was administered during a suprapubic cystotomy and resection of a papilloma of the bladder of a man aged 46. On the third day after operation, signs of pneumococcic meningitis developed, and the patient died of meningitis and lobar pneumonia on the fifth day. The 24 cases in which death occurred in this series included those in which it occurred during the time of administration of the anesthetic or during the operation as well as those in which the patient survived the operation and did not die until some time later in his stay in the hospital.

A preliminary dermal injection of ¾ grain (0.048 Gm.) of ephedrine and procaine hydrochloride was used. The drugs employed in this series included procaine hydrochloride, nupercaine, *p-n*-butylaminobenzoyl-*di*-methylamino- ethanol hydrochloride and a proprietary procaine preparation. In the majority of cases, particularly in those in which the time of operation did not exceed seventy-five minutes, from 100 to 150 mg. of procaine hydrochloride was used. In cases in which the operating time was expected to exceed seventy-five minutes, 200 mg. of nupercaine was used in the early cases. This drug was soon discarded in favor of 22 cc. (20 mg.) of *p-n*-butylaminobenzoyl-*di*-methylamino-ethanol hydrochloride because of the delirium which developed soon after anesthesia and which lasted from six to twelve hours in 3 of the cases. In Abeshouse's experience, spinal anesthesia has proved to be excellent for operations on the genito-urinary tract.

UROGRAPHY

Mertz and Hamer [57] stated that lateral pyelography is practical and can easily be performed on the ordinary x-ray cystoscopic table without added discomfort or risk to the patient. The renal pelvis and ureter can be satisfactorily visualized in the majority of cases. A study of the lateral pyelogram should include the vertical and anterior position of the kidney, the degree of horizontal and vertical rotation of the kidney, the outline of the pelvis as compared to that in the anteroposterior pyelogram and the course followed by the ureter. Mertz and Hamer stated that their cases have been too few to establish general rules of interpretation, but they believed that their experience was sufficient to justify bringing the subject to the attention of others.

57. Mertz, H. O., and Hamer, H. G.: The Lateral Pyelogram: An Investigation of Its Value in Urologic Diagnosis, J. Urol. **31**:23 (Jan.) 1934.

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